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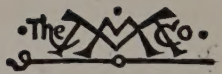
A BIPOLAR THEORY OF LIVING PROCESSES



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A BIPOLAR THEORY OF LIVING PROCESSES

BY

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EDITED BY

AMY F. ROWLAND

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To
BOB

PREFACE

This volume represents an attempt to present certain conclusions which are based upon researches which have been in progress continuously from their initiation in 1898 to the present time. The progress of these studies and the development of the theory which is based upon them are summarized in the introduction.

An attempt has been made to include in the bibliography the titles of the publications which we have found especially valuable in the development of the bipolar theory. It is obviously impossible, however, to include the name of every author from whom we may have gained information or suggestion which has been of direct value in the development of the theory here presented.

The names of the many collaborators who have been associated with me in these studies have been mentioned in previous publications, or are cited in the text of this volume, but I should like in addition to express here my sense of indebtedness to all who have shared in the experimental details and in their interpretation and presentation.

G. W. C.

Cleveland, 1925.

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PART I
INTRODUCTION

INTRODUCTION

CHAPTER I

The Development of the Bipolar Theory

When I was a student in medical school I came for the first time in contact with the dramatic picture of failing bodily energies and death. The patient was young and strong; every organ of his body was sound; he had lost but little blood although both legs had been crushed by a locomotive. As I watched him slowly sink into death, the mental and physical prostration, the shrunken, pallid face, the cold sweating skin, the fading pulse, fixed the picture in my mind. Autopsy revealed no lesion in any vital organ. Immediately I planned a research for the purpose of attempting to find what essential mechanism had failed. As I had watched the pulse fading so inevitably I thought that death was due to the want of circulation as the result of heart failure; but what had caused the heart to fail? It was not hemorrhage, but it appeared to me that failure of the circulation, to whatever it was due, must have been the primary cause of death, and this belief directed the course of my initial studies.

After futile experiments in an improvised laboratory in Cleveland I was fortunate enough to secure an opportunity in 1895 to pursue this research in the University College of London under the direction of Sir Victor Horsley. Since that time this study has proceeded without interruption in London, in Cleveland, in war hospitals in France, at the Western Reserve University Medical School, at Lakeside Hospital and in the Research Laboratories of the Cleveland Clinic Foundation. During this long search for the underlying causes of fatigue, exhaustion and death, data were accumulated which made it apparent that to understand the nature of exhaustion and death,

it was necessary first to understand the nature of life itself. The research therefore turned from a study of the nature of death to a study of the nature of life. In the progress of these studies there have been four principal stages:

I. Studies of the Circulation and Respiration.
II. Studies of the Blood Chemistry.
III. Cytological Studies.
IV. Biophysical Studies.

I. Studies of the Circulation and Respiration

Neither the heart nor the circulation nor the respiration was found to be the primary factor in the causation of exhaustion and death from surgical shock. Nevertheless, three outstanding facts of great clinical and scientific value emerged from these long negative studies of the circulation—negative in that they failed to identify the mechanism the failure of which leads to fatigue, exhaustion and death.

1. It was established that nerve blocking prevents surgical shock.
2. The technic and value of the direct transfusion of blood was established.
3. It was found that stimulants, as a class, increase fatigue and exhaustion; that morphin minimizes fatigue and exhaustion.

Another finding of scientific interest but of little practical value was the resuscitation of the dead by adrenalin under certain limited conditions. It was found also that there was a wide range of variation among the various tissues and organs of the body in their resistance to death. The two organs which most promptly succumbed were the brain and the liver, the heart muscle and voluntary muscle being approximately one hundred times more resistant. It appeared, therefore, that these two master-tissues must be the key structures.

Having found that the changes in the circulation and the respiration which are present in exhaustion and death are end-effects and not primary causes, it seemed probable that the pri-

mary cause of exhaustion must be some change in the blood chemistry.

II. Blood Chemistry Studies

In association with M. L. Menton, and W. J. Crozier, the chemistry of the blood in exhaustion was investigated. The reserve alkalinity was first studied with the thought that it might be diminished in exhaustion, but with negative results; then the hydrogen ion concentration was measured with the thought that it would be increased in exhaustion, again with negative results. From these studies, however, came a finding of great clinical importance—namely, that all inhalation anesthetics cause a progressively increased hydrogen ion concentration, death occurring at the moment when a neutral point is reached and a positive acidity established. This finding showed clearly that *the acid-alkali balance of the organism has a vital significance.*

Having failed to discover the fundamental cause of death in the circulation, the respiration or the blood, we turned to a new line of attack upon the problem—a line suggested by Hodge's studies of changes in the ganglion cells of the honey-bee in fatigue.

III. Cytological Studies

In collaboration at first with D. H. Dolley, later with J. B. Austin and F. W. Hitchings, the cells of every organ and tissue of the body including the red blood cells were studied in animals in excitation, in exhaustion and after death from every conceivable cause. In this research, which lasted for nine years, we for the first time glimpsed a fundamental fact of first importance. First of all, these studies led to the conception that there is in the organism a kinetic system, the several organs of which collaborate in the transformation of potential into kinetic energy in the form of adaptive responses —muscular action, emotional excitation, febrile phenomena, etc.

In spite of our array of facts, however, we still were un-

able to formulate any hypothesis whereby to explain the vital rôle of the liver; and yet if our cytologic researches were of value, the rôle of the liver must be identified, for in these studies changes in the cells of the liver appeared consistently with the changes in the cells of the brain. In the hope of discovering the nature of the interrelationship of the brain and the liver we considered the structure of the cells, especially the following facts:—(1) that differential stains were required to define the nucleus and the cytoplasm, the nucleus taking a basic stain, the cytoplasm an acidic stain; (2) that in exhaustion and death from any cause, even including the want of sleep, the differential stainability of the cells of the brain and of the liver was decreased or even disappeared; (3) that after the administration of a fatal dose of an alkali the differential stainability of the cells was lost; (4) that after the administration of a fatal dose of an acid the differential stainability of the cells was lost. When these observations were considered together with the fact that when the alkalinity of the blood disappears—that is, when the neutral point is reached—the animal dies, it became evident that death was associated with loss of the acid-alkali balance within the cells of the organism. What could be the vital relation between the relative acidity of the nucleus and the alkalinity of the cytoplasm? An acid colloid and an alkaline colloid separated by a semi-permeable film, a dielectric membrane, constitute an electric cell within which an electric potential exists between the positive and the negative poles. According to this conception the cells of the organism would be electric cells in which the comparatively acid nucleus would be the positive pole and the comparatively alkaline cytoplasm the negative pole. At this point, therefore, we began to consider the organism as a bipolar mechanism and to direct our researches into the field of biophysics.

IV. Biophysical Studies

According to our cytological findings it would seem that the maintenance of the acid-alkali balance between the nucleus and the cytoplasm of the cells—electric potential—is essential to

life and furnishes the energy of the living process itself. Its reduction to zero or equilibrium is death.

It remained to discover how this vital potential is maintained, and we assumed that the potential was due to oxidation and that in turn the electric potential within the cell was the physical catalyst that governed oxidation. This assumption led us to abandon physiological, chemical and microscopical methods of attack upon our problem and to turn to physics in the hope that by the application of physical methods we might identify the physical laws in accordance with which the organism is operated. Accordingly, in 1917, in collaboration with G. B. Obear, Amy F. Rowland, and Helen Hosmer, a series of researches was initiated which led to the establishment of a permanent biophysical laboratory in which the bipolar theory has been subjected to biophysical tests.

Our histological studies had indicated that the lipoid films surrounding the nucleus and the cytoplasm offered a definite resistance to the positive hydrogen ions and that in death this resistance was lowered. If this inference was correct, then the changes indicated by the microscope could be more accurately identified by measurements of the electric conductivity of the tissues. Conductivity measurements supported this assumption.

If we were justified in our further assumption that the potential within the cells is maintained by oxidation, then variations in oxidation must accompany variations in activity and these variations in oxidation would be manifested by variations in temperature. This assumption was supported by biophysical tests.

If the organism is operated by electricity, one would expect that the cells would be adapted for the accumulation of electric charges. That this is the case has in turn been shown in our biophysical laboratory by Hugo Fricke.

Following the lead suggested by these findings the organism has been studied as a whole to secure evidence as to the existence of a part of highest and a part of lowest potential, and of electric currents adapted to the vital processes of the organism.

Finally, our findings from our initial study to the present have been scrutinized and correlated for the establishment of a premise which would bridge the gap between the living and

the non-living and suggest a physical line of ascent from the atom to man.

V. Method of Presentation

In this presentation of the theory we shall offer first the argument with a general survey of the supporting evidence. The evidence from histological and biophysical researches and from certain generally accepted biophysical facts has been summarized in Parts III and IV, thus making it convenient for the reader who may wish to escape the tedium of reading these details to pass at once to the conclusion offered in Part V. Certain extensive excerpts from the literature and detailed experimental data have been placed in the Appendix.

PART II

THE ARGUMENT

CHAPTER II

A Bipolar Theory of Life

Any theory of the nature of life must account not only for the common fundamental phenomena of life in all forms of living beings from the simplest to the most complex, but it also must identify the fundamental form of energy to which the reactions of life can ultimately be traced. It must identify a uniform pattern or plan for the transformation and utilization of energy. It must account for the necessity for such ever-present characteristics as the acid-alkali balance, the lipoid films, the omnipresent electrolytes. It must show why a continuous supply of oxygen and continuous oxidation are necessary. It must show the mechanism of stimulation and of specific response to stimulation. It must account for the phenomena of memory. It must account not only for reproduction but also for the transmission of acquired characteristics. It must identify the operation of the unicellular and of the multicellular organism with the operation of protoplasm itself. It must show the mechanism of the creation of living matter—protoplasm—from the energy and matter of the environment.

It is obviously beyond the present scope of human knowledge to meet all these requirements. It is feasible, however, to present a theory which appears at least to point to a reasonable explanation of the essential characteristics of living organisms and of the phenomena of life itself.

Mathews has stated that the difference between the living and the lifeless is a difference in the energy content of the molecules. "The difference between the reactive molecules of protoplasm and the same unreactive molecules outside of protoplasm is a difference in energy content. The various chemical and physical powers of protoplasm which so strikingly differentiate it from the lifeless are due to the increase in the energy content

of the molecules. Living matter contains molecules having a high content of energy and capable of passing to a more stable dead form in which they contain less energy."

The central fact regarding living organisms then is that they are transformers of energy and that they must be operated by means of one or more of the following six forms of energy: (1) heat, (2) light, (3) gravitation, (4) intermolecular forces, (5) chemical energy, (6) electric energy.

It is obvious that the organism of a rabbit, for example, is not operated by heat energy; nor by light energy; nor by gravitational forces; nor by surface energy. It follows that the probable driving force of living organisms must be either electrical or chemical energy, or a combination of both. We therefore propose the theory that living organisms are bipolar electric mechanisms. If this theory is tenable it must meet the following requirements:

1. That electricity is a constant phenomenon of living processes. This has long been known.

2. That the application of electricity to the muscles or glands, or to their nerve supply will cause them to perform their natural functions. This is a basic fact which is universally accepted by physiologists.

3. That the materials of which animals are constructed are specifically adapted to electrical processes. Certain generally known facts regarding the principal constituents of the body will be cited and new evidence submitted.

4. That in structure and function the unit cells which drive the organism not only are adapted to fabricate, to store and to discharge electricity, but that this is true also of the protoplasm itself. Certain generally accepted facts and certain new evidence which tend to establish this requirement will be cited.

5. That the organism as a whole is a bipolar electric mechanism bearing the pattern of the unit cells and that the unit cells are constructed on the pattern of the atom. Experimental data which tend to support this requirement will be offered.

6. That the normal and the pathological phenomena of man and animals can be interpreted in electrical terms. Summaries of experimental researches undertaken to establish this point will be given.

The Electrical Significance of Certain Constituents of the Animal Organism

Water, which forms more than three-fourths of the body content, has the highest known dielectric constant. This property of water is responsible for the ionization of the infinite number of molecules which water holds in suspension or in solution. Water is also one of the most important catalysts.

Electrolytic solutions and colloids which make up the bulk of the body are especially adapted to electro-chemical processes.

Hydrogen ions permeate all living organisms. The slightest change in the hydrogen ion concentration fundamentally alters the organism; and it is known that hydrogen ions are of high electrical significance.

Carbohydrates are the source of the hydrogen ions which are released by means of oxidation.

Of the highest electric significance are the exquisitely thin, low-conducting lipoid films which surround each of the trillions of cells which compose the body. For it is a well-known physical fact that an oil film has a remarkable capacity for the accumulation of electric charges and that the thinner the film the higher its electric capacity. While each of the other essential constituents of the organism might play a rôle in an organism operated by some other form of energy, these lipoid membranes could be significant only in an organism which is operated by electrical forces.

The animal organism as a whole is enmeshed in a network of highly specialized electric conductors—namely, the *nervous system.* In its physical composition, therefore, the body is not only highly adapted to electrical processes but its constituents in their interrelations within the organism could not be of any conceivable value in a mechanism operated by other forms of energy.

The Unit Cell as a Bipolar Mechanism

The unit of structure and of function of the animal organism is the cell. An animal may in fact be regarded as a disperse

FIG. 1.—Photomicrograph of brain cell (× 6000).

system of cell suspensions. It is primarily essential therefore to consider the operation of the cell as a bipolar unit.

The nucleus of the cell is comparatively acid, the cytoplasm is comparatively alkaline; the nucleus and the cytoplasm are separated by a semi-permeable film of very low conductivity. These characteristics of the cell indicate a difference in electric potential between the nucleus and the cytoplasm.

We may therefore consider the cell as a bipolar mechanism, the nucleus being the positive element, the cytoplasm the negative element. The oxidation in the nucleus appears to be on a higher scale than the oxidation in the cytoplasm; and therefore as the electric tension increases in the nucleus, the current breaks through; the potential in the nucleus falls and in consequence the current is interrupted. Since the potential is again immediately restored by oxidation, we conceive that an interrupted current passes continually from the positive nucleus to the negative cytoplasm and in consequence a charge is accumulated on the surface films. These films of infinite thinness and of high dielectric capacity are peculiarly adapted to the storage and adaptive discharge of electric energy.

Why is the extreme thinness of these films of advantage? The work of the cell depends on its capacity for oxidation; oxidation, as we believe, in turn depends on the electric energy seated between the nucleus and cytoplasm; this energy depends on the voltage in the cell and on the electric charge the lipoid films will hold; the electric charge the lipoid film will hold is dependent on the thinness of the film—the thinner the film the greater the charge. Dr. Fricke has found that the film which surrounds the cells is on the order of 4/10,000,000 of a centimeter thick; and that this lipoid film has electric capacity of a high order, viz., 0.8 microfarads per square centimeter.

We may consider then that electricity keeps the "flame of life" burning in the cell; and that the flame (oxidation) supplies the electricity which is the "vital force" of the animal. In accordance with this conception, therefore, the cell is an automatic mechanism; life as we view it is the expression of the activity of this automatic mechanism.

In accordance with this conception, it is of infinite advantage to have the organism made up of trillions of units called cells

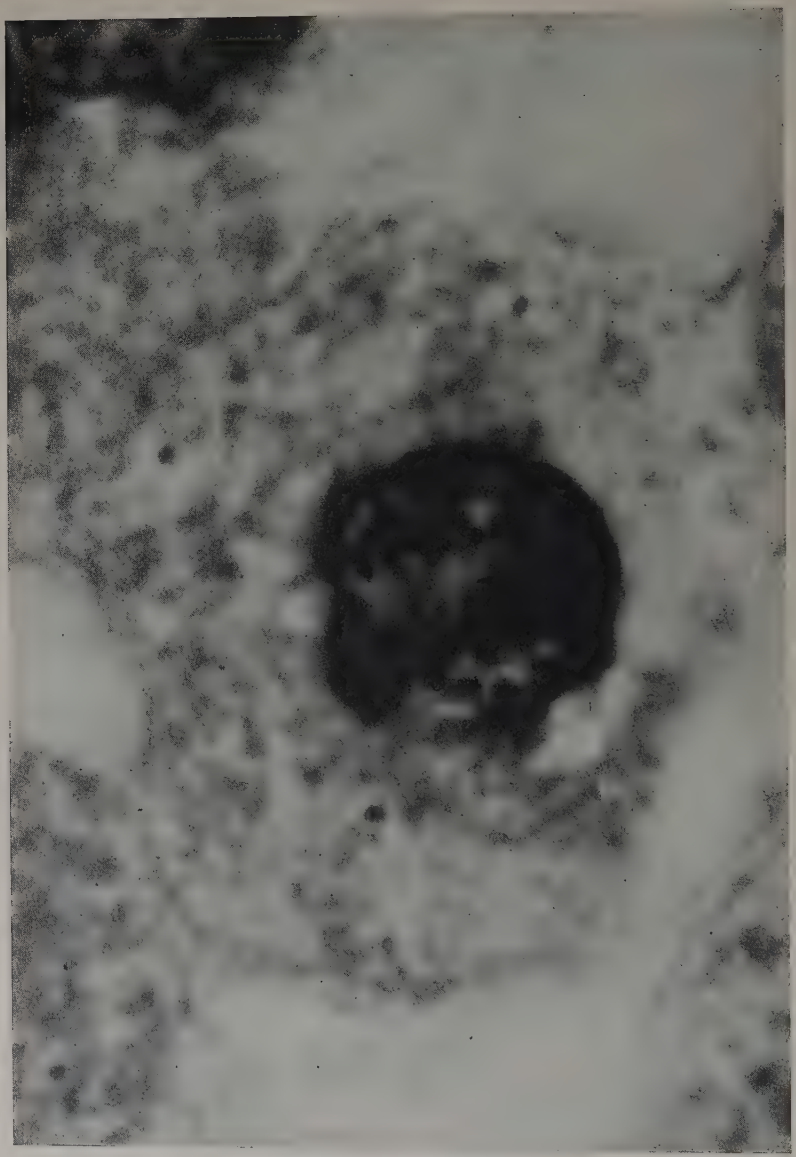

FIG. 2.—Photomicrograph of liver cell (× 6000).

instead of an equal mass in a single unit. The advantage of the greater surface area of the lipoid films surrounding the microscopic cells as compared with that of a single cell of equal mass is the corresponding increase in the amount of the electric charge; a corresponding increase in the amount of oxidation; a corresponding increase in working capacity. Sir Arthur Thomson has estimated that there are 28 trillion cells in the human body. On the basis of even as small an average diameter as 20 microns the total surface area of the cells in the whole body would be equivalent to 9 acres. Meynert estimated that there are 1,200 million cells in the cerebral cortex; thus with an assumed average diameter of 30 microns the total surface area of the cortical cells of the brain would be 3.36 square meters. On the basis of Dr. Fricke's calculation that the electric capacity of the cell membrane per square centimeter is 0.8 microfarads—this total surface area would have a capacity equivalent to that of a Leyden jar made of glass 0.3 millimeters in thickness with a surface area of 114,000 square meters, the area of a city block.

A homely analogy would be a comparison of four surfaces secured for writing by squaring a huge log, as compared with the amount of writing surface secured by converting the log into paper. The crude pattern of nucleus and cytoplasm could be carried out in a large animal with a range of activity comparable to that of a glacier—a log instead of a library.

Furthermore, a consideration of the cell as a bipolar electrochemical unit indicates the dividing line between the living and the non-living. In accordance with this conception, the term "living" applies to the state in which there is an accumulation of electric energy on the membranes with a resultant polarization, together with a mechanism for the release of that energy to perform work. There is no more energy per mass in the living than in the non-living. In the living, energy is captured and stored and made to run the organism—in the non-living the same amount of energy exists, but is balanced; equalized; inert; non-living.

Two streams of water flow swiftly, each seeking the lowest level—equilibrium. One is caught and retarded, thereby building up a potential energy of position as in a mill race; in

its further course this retardation is suddenly released and in the discharge of this acquired potential energy of position a water wheel is turned, and as a consequence of the turning of the wheel, heat or light or electricity is generated. The stream which has thus acquired a difference of potential may be said to live, as compared with the undisturbed river, which takes its course unchecked toward complete equilibrium.

Two different metal plates and a suitable solution as separate units are inert—non-living; immerse the plates in the solution and connect them with wires so that a circuit is formed and a current of electricity capable of doing work is created. This corresponds to the energy function of the living.

According to this conception, the physical energy in the living and the non-living is essentially the same. In one case the energy is static—in the other it is dynamic. In the one the difference of potential is produced outside of the mechanism; in the other the difference is constantly maintained by automatic action within the mechanism itself.

Bipolarism of the Multicellular Organism

The single cell, whether it exists independently as a unicellular organism or as one of the cells of the multicellular organism, is a bipolar mechanism, the nucleus being the positive element, the cytoplasm the negative element.

As the nucleus and cytoplasm of the unicellular organisms are evolved respectively into an association of trillions of cells, thus forming the higher animals, this primary relation between the nucleus and cytoplasm is presumably still maintained among these trillions of cells, some groups of which may be considered as "nuclear" cells, because in them is found the highest oxidative capacity, while others, because of their comparatively low oxidative capacity, may be considered as "cytoplasmic" cells. If our conception be true, then among the positive or "nuclear" tissues there must be a tissue of the highest potential of all, and since oxidation determines potential, we are justified, on the basis of experimental studies, in considering that *the brain is the positive pole* in the organism. It remains to give the evi-

dence on which we base our assumption that among the "cytoplasmic" or negative tissues, the liver has the lowest potential —is the negative pole of the organism.

If the brain and the liver are the positive and the negative poles of the organism, then certain conditions would follow from this interrelationship:

1. The brain and the liver would work together, would to-

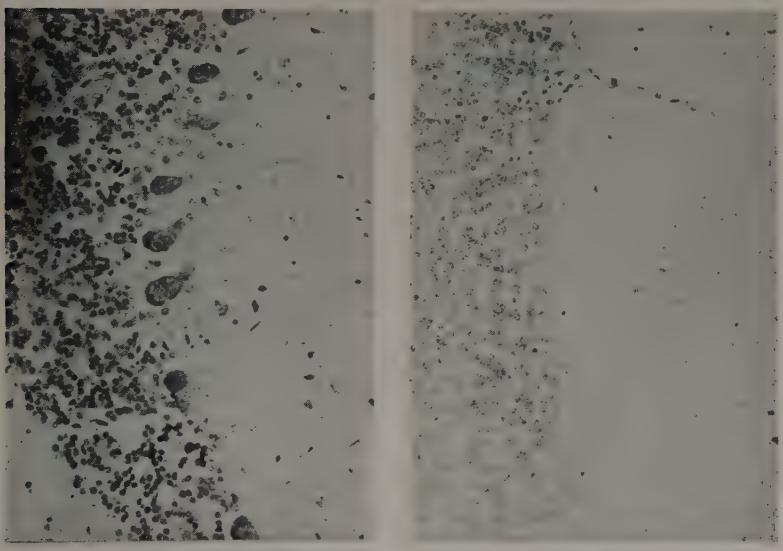

FIG. 3.—Effect of hepatectomy on brain cells. A. Section of cerebellum of normal dog (from photomicrograph × 310); B. Section of cerebellum of a dog after complete excision of the liver (from photomicrograph × 310).

gether show specific changes as the result of work, would together be restored by sleep. This condition has been supported by histological and by physical researches.

2. If the negative pole—the liver—were removed, then the unit cells of the positive pole—the brain—would lose their own potential and the brain would cease to function. This is supported by experimental and clinical evidence. (Fig. 3.)

3. Since in their positive-negative relationship the functions of the brain and the liver are antithetic we would expect that their electric conductivity would vary in opposite direc-

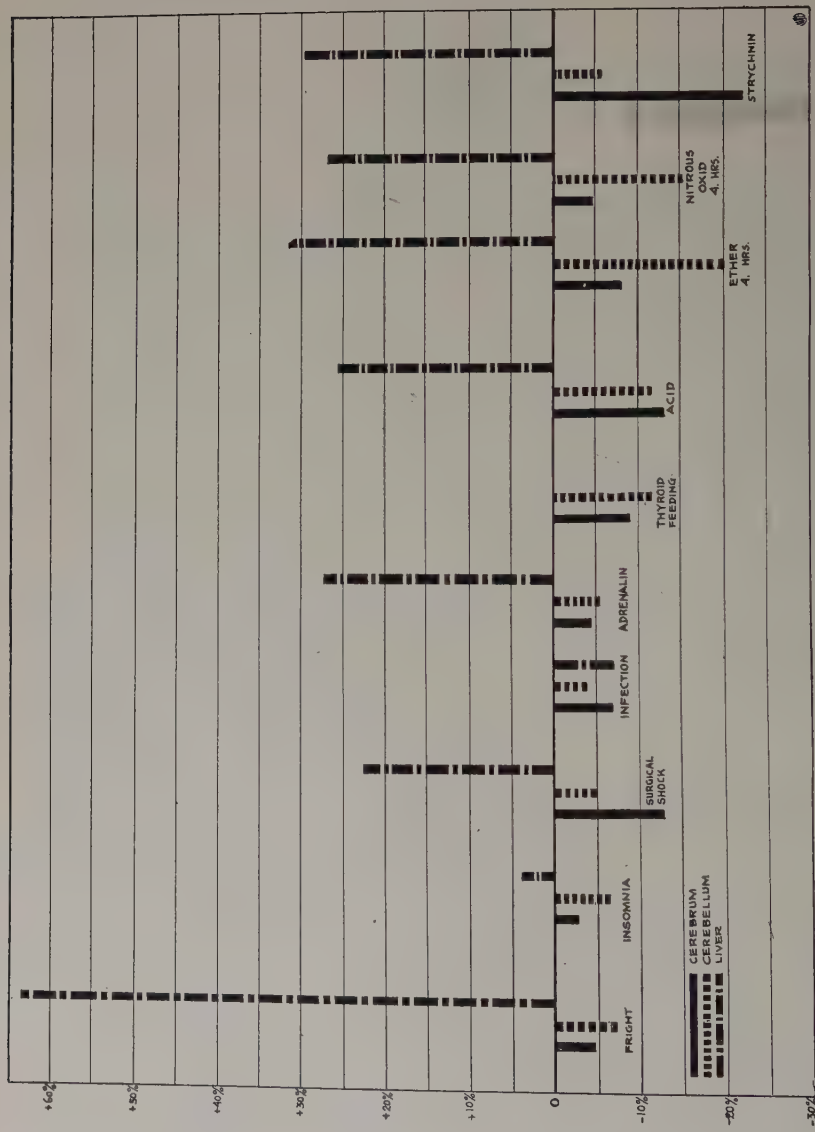

FIG. 4.—Opposite effects of stimulation to the point of exhaustion on the electric conductivity of the brain and the liver. (Percentile variations.)

tions and that the temperature changes due to stimulation would vary in opposite directions. Both of these expectations have been realized by the findings of experimental researches. (Figs. 4 and 5.)

4. It is the negative pole that accumulates waste products and keeps the circuit clear. This is a specific function of the liver.

From these premises we assume that when the great circuit between the liver and the brain is broken, the lipoid membranes, the interfacial surfaces between the colloids, interfaces in the proteins, etc., no longer receive the electrical charges on which their structure and function depend, and coagulation and death follow. Coagulation follows because the infinitesimal particles making up the colloids are no longer held apart by electrical charges. Although, as we believe, the specific activities of muscles, glands, etc., are carried on by minor circuits, nevertheless, unless the grand circuit between the brain and liver be kept intact and active, life cannot continue. According to this conception the organisms of multicellular animals as a whole are wired up in innumerable circuits—the unit of which is the nerve cell and its projected nerve fiber.

The Circuit in the Bipolar Mechanism

As we have already stated, according to the bipolar theory the unit cells are so constructed that the processes of charging and of discharging follow each other in rapid succession, so that an interrupted current passes between the nucleus and the cytoplasm. Thus, in each of the unit cells of the brain, each cell would fire its charge in a rapid volley through the semipermeable membranes, the sequence being first an increase in voltage; then a break through the film; a fall in voltage; an instantaneous rise in voltage; these successive events occurring at infinitesimal intervals, just as is the case in similar apparatus made by man. Since the structure of certain cells of the brain is prolonged into highly conductive intercommunicating axons the sum of the charges of many cells may be conducted through their axons past the synapses to the muscles or glands to be

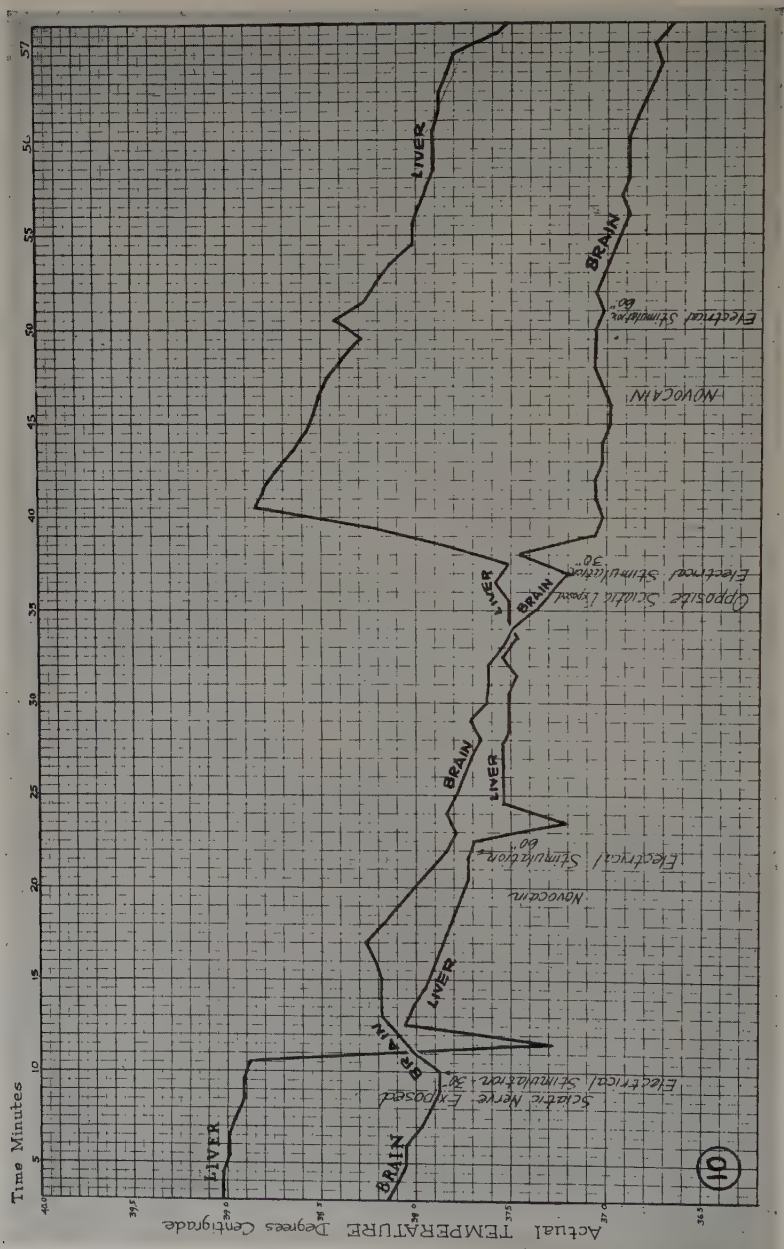

FIG. 5.—The effect of electric stimulation on the temperature of the brain and the liver. Note the opposite effects in each instance when the stimulation is applied.

stimulated. (Fig. 6.) A part of the current, however, may presumably leak through the semi-permeable membranes and may not be consumed in the adaptive response of the muscles or glands. This portion of the current, obeying the universal law

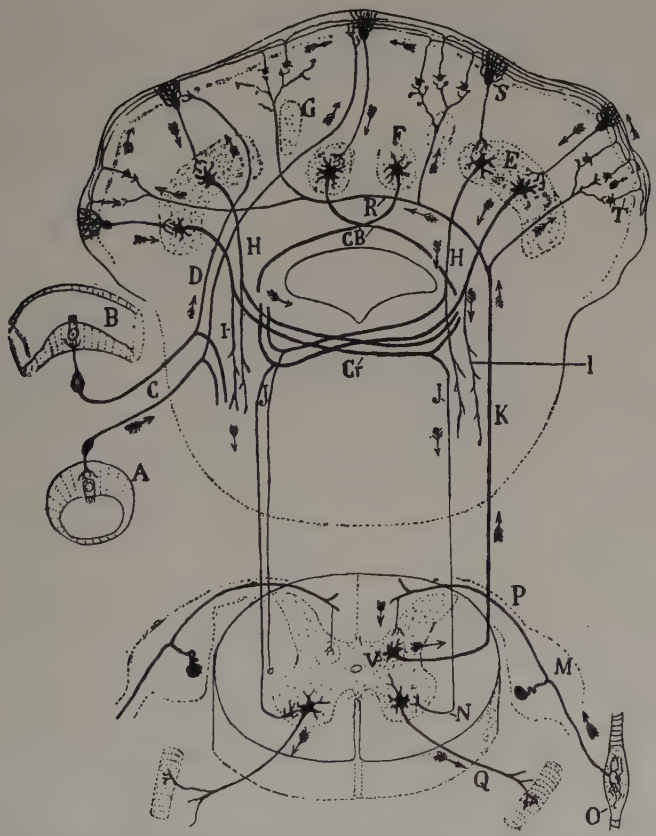

FIG. 6.—Schematic plan of afferent and efferent nerve paths. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 2, p. 144.)

which governs the flow of electricity from the point of highest to that of lowest potential would finally reach the point of lowest potential—the liver—and from thence be conducted back to the brain through the electrolytic fluids permeating the organism. (Fig. 7.) The path from the muscles, glands, etc., to

the liver, possibly may be over the sympathetic nerves everywhere present in the walls of the blood vessels. (Fig. 8.)

The initiation of the energy transforming impulse in the brain and other nerve cells is due to physical forces in the internal and the external environment; that is, chemical impulses in the internal environment, and in the external environment, the physical impulses of light, heat, contact, and sound waves. According to the bipolar hypothesis, therefore, these impulses from within or from without initiate the current which passes over one or another portion of a circuit which in-

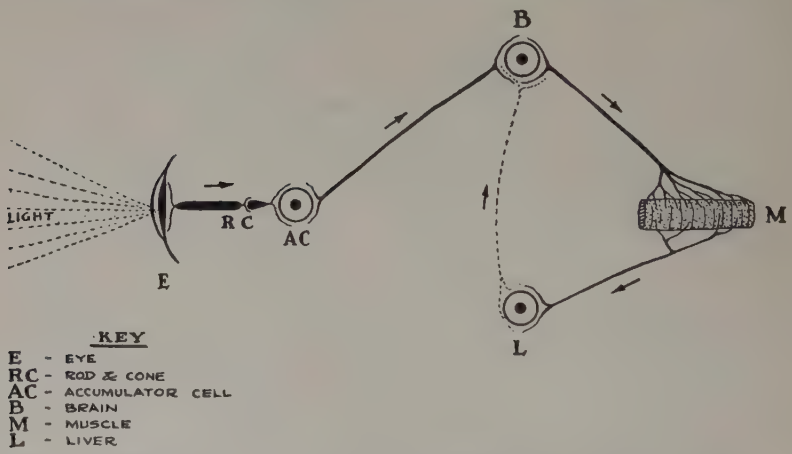

FIG. 7.—Schematic plan of theoretic complete sensory motor circuit.

cludes about twenty-eight trillion electro-chemical units, most of which are self-charging condensers, charged up ready to be discharged by a trigger action, on the arrival of the electric impulse initiated in the circuit by the environmental stimuli. For example, a pattern of white light altered by an object falls on the rods and cones of the eye, which is continuously and in even balance responding to white light. (Fig. 9.) This disturbed balance becomes the adequate stimulus which by a trigger action discharges millions of charged condensers. We may suppose that from condenser to condenser a vast accumulating electric charge passes down through the interrupting synapses, driving muscles and glands to action, with consequences which

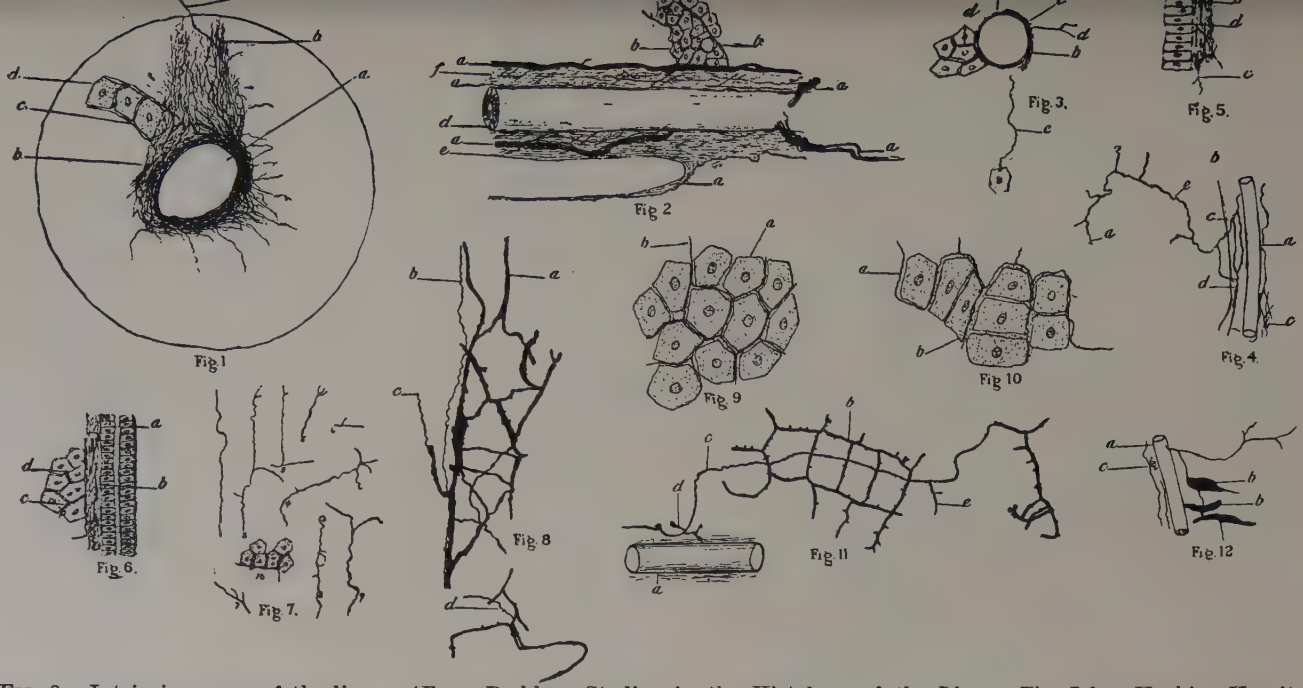

FIG. 8.—Intrinsic nerves of the liver. (From Berkley: Studies in the Histology of the Liver. The Johns Hopkins Hospital Reports, 1895, iv, 231.)

1. Meshwork of fine fibrillæ surrounding a central vein. 2. Drawing from a section not far from the transverse fissure of the liver. 3. Central vein of a lobule with surrounding nerve fibers. 4. Nerves and their branches surrounding a portion of a hepatic artery. 5. Portion of a biliary canal showing at C nerve fiber with a forked termination at D. 6. Biliary duct with nerve fibers and inter-cellular branchings. 7. Varieties of nerves and terminations. 8. Portion of a coarse biliary plexus along the margin of an inter-lobular space. 9. Portion of an inter-cellular hepatic plexus. 10. Portion of the terminal distribution of a single nerve fiber. 11. Portion of a biliary plexus. 12. Neural enlargements adjacent to a portal vein in an inter-lobular space.

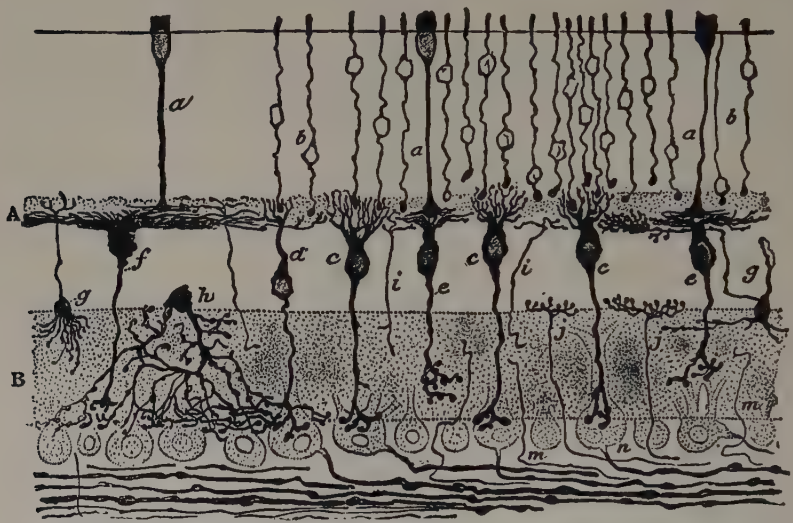

FIG. 9.—The retinal receptive mechanism. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 2, p. 308.)

FIG. 10.—The olfactory receptive mechanism. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 1, p. 116.)

may be commonplace or dramatic. The audion of the wireless, the stepping-up mechanism of the long distance telephone, are but weak imitations of the marvelous augmentation and step-up mechanism which probably exists in the human brain.

Electricity, it would appear, is the thread which binds together in form and function the compound, the solution, the colloid, the protoplasm, the cell, the animal.

A Bipolar Interpretation of Normal and Pathological Phenomena

If the bipolar theory is correct, then it must interpret the abnormal as well as the normal phenomena of animals and man. Thus, it must interpret in electro-chemical terms such major phenomena as the emotions, physical exertion, etc. It must interpret the effect of physical and chemical injury; the effect of want of oxygen; of want of water; the effect of too much, no less than of too little heat; the defense against bacteria; the process of healing of wounds; the effects of anesthetics, and of the various drugs; the phenomena of hyperthyroidism and of thyroid deficiency; the phenomena of excessive adrenal activity and of adrenal insufficiency.

It must interpret the difference in physical mechanism between a fertilized and a non-fertilized cell; between a cancer and a normal cell; it must show the mechanism of stimulation and of depression; it must interpret shock, exhaustion and death; it must interpret sleep and restoration. While all of these interpretations have not been made as yet, the data thus far accumulated present such uniformly supporting evidence that we believe the basic evidence whereby to interpret most if not all of the phenomena of life will ultimately be secured.

Since electric conductivity and the production of heat are basic phenomena in the operation of a bipolar mechanism, we have tested the theory by measurements of changes in electric conductivity and of heat production in various organs and parts of the body.

In accordance with the bipolar theory we would expect:

1. That the electric conductivity of cells would vary with stimulation and depression.

2. That the conductivity of the part of highest potential (the brain) and the conductivity of the part of lowest potential (the liver) would vary in opposite directions.

3. That physical or emotional excitation, excitation pro-

duced by the intravenous injection of adrenalin, by physiologic doses of iodin or of thyroid extract, or by the injection of strychnin would show in the brain an increased conductivity in the stage of excitation and a diminished conductivity in the stage of fatigue, and antithetic effects in the liver.

4. That ether anesthesia in its early or excitant stage would show an increased conductivity, and in the depressant or anesthetic stage a diminished conductivity of the brain.

5. That morphin would minimize or prevent changes in electric conductivity due to the action of adrenalin; of infection; of physical injury; of emotional excitation.

6. That the excision of the liver or of the adrenals would decrease the conductivity of the brain.

7. That prolonged consciousness carried to the state of fatigue would decrease the conductivity of the brain and that sleep would restore the normal conductivity.

8. That the actively multiplying cancer cells would show a higher conductivity than the normal cells of the tissue in which they arose; that the central autolyzing, non-growing part of a cancer would have a lower conductivity than the aggressively growing margin of the cancer; that such precancerous tissue as X-ray scars, adenomata or fibroid tumors would have a conductivity higher than that of normal tissue.

9. That such mediating fluids as blood, cerebrospinal fluid and bile would have a high conductivity.

All of these expectations have been realized by the test of electric conductivity measurements.

Having found that the changes in electric conductivity were consistent with the bipolar theory, we then by means of sensitive thermocouples made simultaneous observations of the temperature changes in the various organs and tissues that might be concerned in energy transformation under the same normal and pathologic conditions as those studied in the foregoing conductivity experiments.

Since according to our theory oxidation is the source of the difference in potential, and since heat is a constant by-product of oxidation, we would expect to find that the temperature of the brain would be increased by stimulants and decreased by depressants.

We would expect to find that stimulation would produce opposite effects upon the temperature of the brain and of the liver and other relatively negative organs. Upon testing these assumptions we found that the temperature of the brain was increased and that of the liver and other negative organs was decreased or unchanged in the acute stage of stimulation by emotion, by physical injury, by strychnin injection, by the injection of adrenalin, when the output of adrenalin was artificially increased by asphyxia, in the excitant stage of ether anesthesia.

On the other hand, if we were correct in our assumption that the liver is the center of negativity and is essential to keeping the circuit in the bipolar mechanism free from chemical by-products, then if the liver were removed, we would expect that the circuit in the bipolar mechanism would become progressively interfered with, and would finally be completely blocked with the resultant establishment of equilibrium or death. We found by experiment that when the great circuit which energizes the organism was broken by the removal of the negative pole—the liver—the temperature of the brain steadily fell until death occurred; also that when stimulants such as adrenalin were given, heat production (oxidation) within the brain bereft of its negative pole was almost or entirely prevented.

Again, in accordance with the bipolar theory, we would expect to find a steady fall in the temperature of the brain, when the semi-permeable films around the cells, the charges upon which govern the oxidation, were rendered less permeable. We found that in the state of deep ether anesthesia, which lessens the permeability of these films and hence interferes with oxidation, the temperature of the brain and of the liver fell steadily until death occurred.

On the other hand, we found that in nitrous oxid anesthesia, which interferes with oxidation itself, but does not interfere with the permeability of the lipoid films surrounding the cells, the temperature of the brain decreased much more slowly.

We found also that sodium, which increases permeability, and calcium, which decreases permeability, having opposite physical effects, had opposite effects on the temperature

of the brain, which was increased by sodium, and decreased by calcium.

We expected to find that in strychnin convulsions we would see violent changes in the temperature of the brain and of the liver; and our expectation was realized.

Since morphin stabilizes the organism, since one of the clinical effects of morphin is the elimination of emotion, and since the emotions probably excite the adrenals to increased activity (Cannon), we expected to find that if an animal were first deeply narcotized with morphin, then given adrenalin, the morphin would lessen the change in the temperature of the brain which is produced by adrenalin in normal animals; and our expectation was realized.

Since the intravenous injection of adrenalin causes an increased oxidation, and since asphyxia causes an increased output of adrenalin, then if an animal were asphyxiated, we expected that the consequent increase in the output of adrenalin would increase the temperature of the brain; and our expectation was realized.

On the other hand, if both adrenal glands were first removed, then asphyxia could produce no increase in adrenalin, and in consequence we expected that in an adrenalectomized animal asphyxia would not cause any increase in the temperature of the brain; and our expectation was realized.

The first effect of a lively hemorrhage is to call out an emergency increase in adrenalin (Cannon). We therefore expected that in an acute hemorrhage the temperature of the brain would show a temporary rise; and our expectation was realized.

These observations on so fundamental a group of facts as the expected variations in temperature and electric conductivity run parallel with another great group of observations which are just as fundamental, but have a much larger chance of error. I refer to the microscopic changes in the size and in the differential stainability of the cells of the leading organs of the body in excitation and fatigue. These carefully studied changes in the cells suggested the bipolar theory. In these experiments we found that vital function varied with the differential stainability of the cells of the brain and of the liver and to a lesser degree of the cells of the adrenal cortex. If the acid-

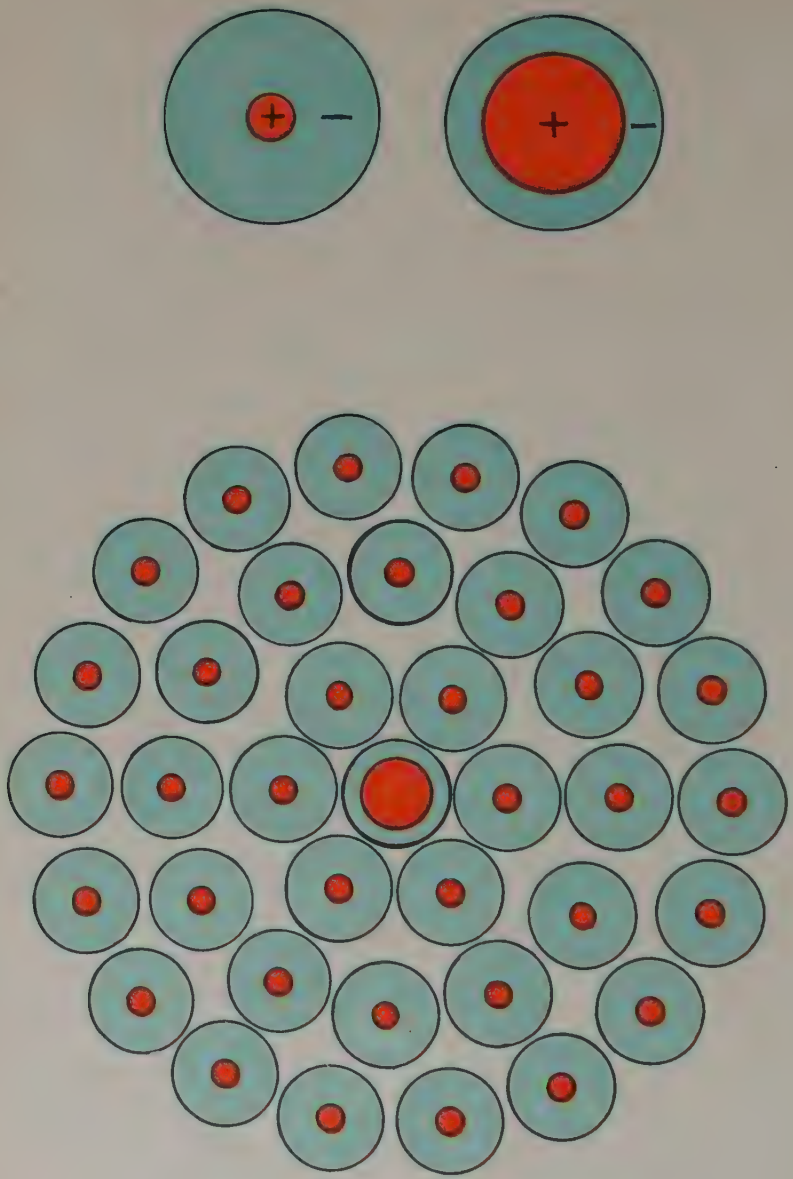

Fig. 11.—Schematic representation of the comparative nucleus-plasma relationship in normal and in cancer cells.

alkali stain of the nucleus and of the cytoplasm respectively is a measure of the respective intensities of the acid or nuclear part of the cell and of the alkaline or cytoplasmic part of the cell, and if the energy of the organism is dependent on the difference in potential and the difference in potential is due to the relative acidity and alkalinity, then the cytologic studies by Dr. Austin, Dr. Hitchings and myself strongly support the electrochemical or bipolar theory.

A Suggestion as to a Possible Bipolar Basis of Reproduction

If oxidation in the cells is due to the electric potential, and if oxidation and the film condenser are essential to life, then it would appear that the potential can be handed on only by a division of the cell, the division of the cell including a division of the mechanism which creates the potential in such a way as to provide in each new cell a difference of potential; i.e., the "flame of life" must necessarily be handed on from cell to cell. Thus, we may conceive that when the spermatozoön which has the characteristics of a nuclear structure is added to the nucleus of the ovum, a greatly augmented nucleus is formed with a corresponding increase in oxidative capacity; hence a capacity for attracting and using food—increasing in size—and in consequence multiplying by cell division.

A Bipolar Conception of the Development of Cancer

By analogy we may conceive that the facilitation of cell division in cancer depends, in some way as yet unknown, upon an increase in the relative size of the oxidative or nuclear part of the cell as compared with the lack of a like change in the neighboring cells. Such an increase in oxidative capacity would add to the bulk of the cell, just as the increase in oxidative capacity in fertilization increases the size of the ovum. (Fig. 11.) By the division of both the nucleus and the cytoplasm the relatively high electric potential would be handed on to the daughter cells, in which in turn the potential would be correspondingly high and thus the process would become progressive

at the expense of the neighboring cells. Thus, in the case of a group of cells which have been injured by repeated slight trauma, or by irritation of any kind so that the cells are alternately injured and repaired, we may suppose that one cell may have become fused with another and lose a part of its cytoplasm; or that by other means the oxidative capacity of the nucleus as compared with that of the cytoplasm may have been increased with a resultant increased size of the nucleus and hence increased potential. This cell would then multiply at the expense of its neighbors and a cancer would develop.

A Bipolar Interpretation of the Rôle of Sleep

If a battery is made to work continuously by keeping its circuit closed, polarization of the plates will take place and the battery is said to be exhausted, which means that the difference of potential has diminished or disappeared. It would appear to be more than a mere analogy that such is the mechanism whereby prolonged consciousness unbroken by sleep leads to exhaustion and death.

If the period of work, i.e., if the passage of electric current is short, as in a single heart-beat, then the degree of polarization is *proportionately small.* The small degree of polarization which results from a single heart-beat requires a proportionately short time for depolarization or sleep, i.e., the pause in the heart cycle may be regarded as its period of sleep. The heart, with its nerve mechanism, takes normally from seventy to ninety naps a minute, and thus is kept depolarized or rested as it works.

We may suppose that the nerve cells which operate the respiratory mechanism become depolarized, or sleep, from sixteen to eighteen times per minute and that thus the respiratory mechanism is kept depolarized or rested as it works.

The salivary glands, the intestinal nerve-muscle mechanism, the digestive glands, etc., we may suppose have alternating periods of *work and polarization,* and of *sleep and depolarization.* Regarded superficially, the functions of respiration, of circulation, of digestion, carry on as if they never rested, never slept; but their sum total of short periods of sleep is relatively

as long as the total period of sleep of that part of the brain whose work creates consciousness, and therefore spends no more time in sleep, but sleeps more continuously.

As for the portion of the brain which governs conscious activity, the periods of work, and therefore of polarization of

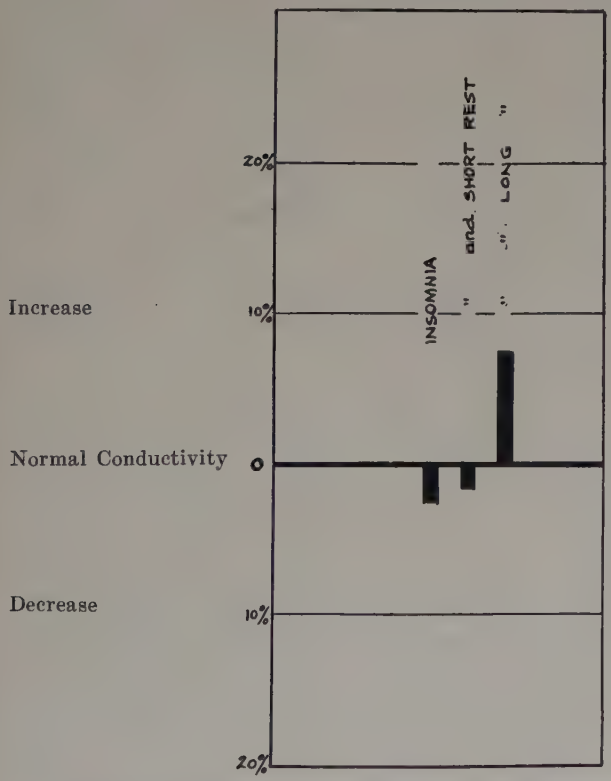

FIG. 12.—The effect of prolonged insomnia and of insomnia followed by a period of rest on the electric conductivity of the brain. (Percentile variations.)

the cells that supply the electric power for consciousness, for emotion and for muscular action, are longer than the periods of work demanded by the heart, by the respiratory mechanism or by the digestive mechanism. Thus the option of evolution apparently has been to run the organism on long shifts or shorter ones.

If the changes in the nerve cells seen in fatigue from various kinds of work and from prolonged enforced consciousness are identical in appearance; if these physical changes are restored only during sleep; and if the degree of cell change varies with the amount of work done at a stretch without sleep—that is, with the amount of electric energy that has originated in or traversed a given cell—then it would require more time and deeper sleep to restore the electrical balance of the cell after prolonged heavy muscular exertion than after a day of restful quiet. And this is demonstrated by experience. It would appear that the degree of exhaustion equals the protraction of consciousness multiplied by its intensity.

Sleep, being a negative phase, cannot be compelled. Consciousness, being a positive phase, can be compelled, even unto death. Normal man cannot sleep unto death; he can sleep only to restoration—no more.

The Relationship of the Bipolar Theory to Surgical Mortality

If the bipolar theory is correct then it must stand the crucial test of the clinic not only in the interpretation of pathological processes but also in the indication of methods of conservation and restoration. If the operation of the organism can be interpreted by the laws of physics, then methods for the protection and restoration of the organism should be dictated by the same laws. For the optimum operation of the bipolar organism, the maintenance of an optimum difference of potential, the following conditions are essential:

1. An abundant supply of water.
2. An abundant supply of oxygen delivered to the cells.
3. Maintenance of the semi-permeability of the lipoid cell membranes.
4. Maintenance of an optimum temperature.
5. Maintenance of the integrity of the poles of the organism, that is of the cells in the brain and the liver.
6. Sufficiently long and sufficiently frequent periods of sleep.

The practical application of these principles in the treatment of the "bad risk" patient may be briefly outlined as follows:

1. Water is given in abundance by every route; 2000 to 4000 c.c. or more given by hypodermoclysis most quickly reaches the cells.

2. Oxidation is promoted by the maintenance of an adequate circulation, by transfusion if the volume of blood is below normal, and by digitalization to strengthen the myocardium if the minute volume is diminished by a weakened myocardium.

3. The semi-permeability of the cell membranes is conserved by the avoidance of ether anesthesia and the employment of nitrous oxid-oxygen analgesia—*not anesthesia*—plus local anesthesia.

4. An optimum temperature is secured by the obvious measures indicated by the needs of the individual case. Of peculiar value are large hot packs over the abdominal viscera, or the application of diathermy during the operation itself. The administration of hot fluids by mouth not only supplies local heat and water but, as experiments have shown, its effects are instantly manifested by increased oxidation in the brain.

5. The integrity of the brain and the liver is kept from further damage by environmental control; by the infliction of minimum trauma; in certain cases by performing the operation in the patient's room; and above all by securing adequate sleep and rest. The protective effect of morphin in particular is needed and when that is contra-indicated other narcotics and sedatives should be utilized to promote the urgently needed periods of depolarization. The fundamental necessity is the maintenance of a difference in potential—this is the maintenance of life.

CHAPTER III

Previously Conceived Theories or Established Facts Regarding Certain Electrical Processes in the Organism

That electro-chemical processes play an important rôle in the phenomena of life has long been held by biophysicists and physiologists. The *similarity* of the nerve or action current to an electric current seems to have been observed by the physicists as soon as the characteristics of the production and conveyance of electric currents began to be recognized.

In 1835, a French physicist, Becquerel, included a section on the action of electricity on organic bodies in an experimental treatise on electricity and magnetism [1] and from the evidence he presents draws the conclusion:

"These facts are sufficient to show that electricity probably plays a great rôle in the animal economy; and that it should also be included among the means whereby life is maintained in organized bodies. But in what way do these bodies, when they begin to develop, put into action this electric principle whose action persists throughout their life? Of this we are completely ignorant. This is, without doubt, one of the mysteries of creation, which man will never be able to fathom."

Of special interest are Becquerel's observations of the phenomena presented by different varieties of electric fish:

"If one shall some day discover that the electric fluid plays a part in the phenomena of life, it will be by studying the peculiar property possessed by certain fish, whereby when they are touched by the hand they produce a reaction similar to that produced by the Leyden jar, and by meditating on the conclusions one can draw therefrom to be applied to physiology in general."

Becquerel reports Galvani's experiments on the electric fish which showed that when connection between the brain and the electric organ was broken, the fish could not deliver a shock; a fact also established by Spallanzani:

"1. We think therefore that the electricity is fabricated in the brain under the control of the will.

"2. In our opinion the difference between the electric fish and other animals is that in the former nature has placed organs designed for condensing the electricity which emanates from the brain, augmenting its tension in such a way as to make of it, as it were, an offensive arm; whereas in the latter this same electricity has only the tension necessary to produce natural contractions and to accomplish the various functions which are expected of it."

Becquerel not only believed that voluntary muscular action is due to electrical action but he advanced the theory that the chemical changes within the organism are also due to electrical action:

"It is not enough to advance the opinion that the organic functions operate under the influence of electric forces, it is necessary also to try to prove this by showing that there can exist in the body electric currents which are capable of producing chemical changes."

Of striking interest is the citation of researches on the acid-alkali reactions of the body by Donné, who made the following conclusion:

"Electric currents exist in animals at the surface of the membranes and in the various organs. This theory rests on the principle that when two bodies, one acid and the other alkaline (or each one playing that rôle in their reciprocal reactions) are separated by a membrane, a multitude of electric currents continually work through this intermediary.

"Electricity acts in two ways within the animal economy. It may produce contractions and other derangements of the equilibrium of the organic parts or it may control the chemical reactions which either promote the secretions or are prejudicial to their production."

It is not until within comparatively recent years that much corroborative evidence in favor of the bipolar theory has been added to these earlier findings and observations. The following observations and conclusions indicate the present trend of thought among many investigators:

Du Bois Reymond held that the action current is an electric current; Crehore and Williams [2] put forward strong evidence in favor of the identity of the action current and electricity. Burdon-Sanderson [3] demonstrated that motor plants such as Venus's Fly Trap and the Sensitive Plant show electric variations during their specific response to stimulation; Waller [4] extended these observations and called these electric variations "blaze currents of action." Bose [5] has found evidence of the identity of vegetable and animal activity, and by most ingenious experiments has shown that electrical phenomena attend the activities of plants, concluding therefrom that electricity plays an important rôle in the vital phenomena.

Piper [6] showed that sound waves originate an electric current in the auditory nerves of fish; Loeb [7] has shown by what physical and chemical processes rays of light orientate the simpler animals; Steinach [8] has identified the electric mechanism by means of which the fish maintains its equilibrium. Einthoven and Jolly [9] and others have confirmed the discovery made by Holmgren in 1866, that when light falls on the retina an electric current is produced in the optic nerve. Bovie,[10] by brilliant experiments has carried this work into newer fields.

Gotch and Horsley [11] have shown that during electric stimulation of the cortex, causing muscular action of the leg, a sustained electro-motive force is present in the spinal cord during the continuance of the stimulation. Not only did they demonstrate the presence of an electric wave, but they were able also to identify the conduction paths in the spinal cord over which this wave travelled, thus showing the intricate pathway along which the current found its way from the cortex to the muscles. Gotch and Horsley also demonstrated a persistent negative variation in the cord during electric stimulation of the Rolandic area.

Nernst [12] supposed that the electrolytes in the axis cylinder lie within membranes which are impermeable to certain ions,

and that when an electric current is passed through a nerve it is conveyed by the dissociated electrolytes, causing an accumulation of positive ions at one point and of negative ions at another. When the concentration reaches a certain point excitation occurs. A. V. Hill [13] supports Nernst's general theory; McClendon,[14] Bayliss,[15] Lillie [16] and others take a similar view.

By microchemical methods Macallum [17] showed that since it contains a greater concentration of electrolytes, the axis cylinder is a better conductor than the medullary sheath.

Meyer [18] found that alteration in the concentration of the electrolytes in the sea-water in which the nerve of a marine animal was suspended altered equally the rate of electric conductivity of the water and the rate of nerve conduction.

Tashiro [19] has demonstrated that as the result of the passage of the normal action current down a nerve fiber, carbon dioxid is given off and oxygen is consumed. Moreover, whether in the case of a normal or an applied electrical current, no heat is produced. A. V. Hill [20] has confirmed Tashiro's findings as to the absence of heat.

R. S. Lillie [21] has developed an analogy between the local electrical effects in metals and in living tissue, as exemplified by the passive state in metals and by nervous conduction in tissue. He considers that the phenomena in each case are due to the formation of local electrical currents, resulting in the case of metals, from local changes in surface tension; and in nervous tissue, from local changes in the permeability of the surface film or membrane. In each case the phenomena are subject to rapid "spreading" depending on the rate of the reaction which initiates it. He states that in nerve tissue "a relation of direct proportion should thus exist between the electric conductivity of the medium and the rate of propagation of the excitation wave."

Howell [22] states that when nerves of one kind are sutured to nerves of another kind, the reaction is determined by the end mechanism; and he states further that efferent nerves are like electric wires—the effect of their stimulation depends on the mechanism found at their ends.

These observations and conclusions are in accord with our

premise, whereby we extend the application of the electric phenomena observed and measured by these and other investigators to include the entire operation of the animal mechanism, and assign to electrical energy the fundamental function of a catalyzing agent by means of which energy is liberated for every activation of the organism.

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CHAPTER IV

The Unit Cell as a Bipolar Mechanism

If every animal organism is a bipolar mechanism, then the unit primary cell in which the life of every individual begins, and each of the constituent cells of the organism at each stage in its development must be a bipolar unit. It seems well to group here the facts regarding the structure and function of the unit cells which are in accord with the bipolar theory, although a general discussion was offered in Chapter II.

The contents of the living cell are divided into two distinct parts by a semi-permeable membrane, and the cell itself is separated from the surrounding fluids by a semi-permeable membrane. These membranes, as we have noted in a preceding chapter, are exceedingly thin; according to Dr. Fricke's finding, they are of the order of four ten-millionths of a centimeter in thickness. On account of its lipoid character such a membrane would have a high capacity for oxidation; and on account of its high dielectric constant, it would have a high capacity for the accumulation of electric charges. If we supplement the calculation on page 17 by a like calculation to include the total number of nerve cells in the central nervous system—3,000,000,000 according to Meynert—the total surface area would be 91.3 square feet. The 10,000,000 large cells of the cerebellar cortex, at an assumed average diameter of 100 microns, would have a surface area of 3.4 square feet. When one imagines the addition to these areas of the total area of the nuclear membranes, and of the lipoid films covering the spherules within the protoplasmic contents of the cells, the enormous capacity of the nervous system for oxidation and for the accumulation of electric charges is at once obvious.

Not only are the contents of the living cell divided into two distinct parts by a semi-permeable membrane, but these two

parts are highly differentiated, as is evidenced by the fact that differential stains are required for their definition. Thus the cytoplasm of the living cells of the multicellular animals, like that of the primal cell which supposedly originated in the alkaline waters of the sea, is alkaline in reaction; the nucleus is comparatively acid. Two colloidal solutions of different reactions, i.e., the one acid and the other alkaline or of different degrees of alkalinity, separated from each other by a selective semi-permeable membrane, constitute an electric cell.

While the above description applies to all living cells, nevertheless cells may vary from each other sufficiently to con-

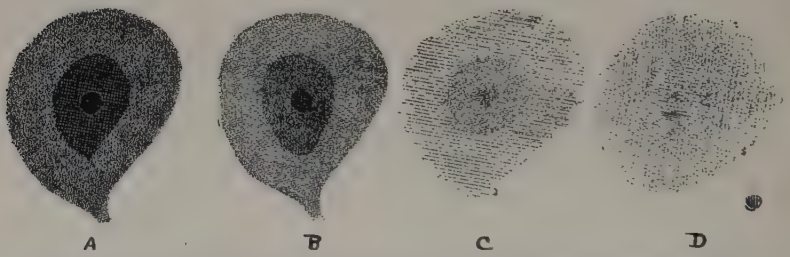


FIG. 13.—Schematic drawing illustrating the progressive destruction of a typical cell. A. First effect of stimulation, hyperchromatism; B. Normal; C. Fatigue. Note the lessening of nuclear-plasma differentiation; D. Complete exhaustion. Note disappearance of nucleus-plasmar differentiation.

stitute distinct groups, or the cells of any one group may vary from each other. In the latter case this variance is evidenced by variations in *functioning power,* in the former by variations in *function.* Whatever the differentiation of functioning power or of function, however, the fundamental characteristics of each cell are universal.

Histologic studies have shown that in non-living cells the nucleus and the cytoplasm have lost to a given degree the power to take differential stains, that is, there is no longer a difference in reaction between the nucleus and the cytoplasm (Fig. 13); and that coincident with the loss of differential stainability, there is an increased permeability of the membranes, with consequent dissolution and disappearance of the cell content.

In addition to the characteristics already cited, the follow-

ing phenomena, most of which have been pointed out by Mathews, are of extreme significance in the consideration of the cells as bipolar units:

At the onset of acidosis, except in the case of the brain-cells, autolytic enzymes appear in the cell, both proteolytic and carbohydrate- and carboxyl-splitting enzymes. That this has a bipolar significance is indicated by the fact that by means of the carbohydrate-splitting enzymes the cells receive the lipoid substances which are essential to the maintenance of the integrity of the lipoid cell-membranes, and, as we believe, to the oxidation whereby the electric potential of the cell is established and maintained.

By means of the carbohydrate-splitting enzymes also anaërobic oxygen is obtained by the cells of all the organs and tissues of the body, except the brain-cells, which depend for their oxidation upon the aërobic oxygen brought by the blood.

As has been stated, it would appear that oxidation and the consequent acidity are parts of the most fundamental processes of the cell, and that variations in the relation between the H-ions and the OH-ions are of fundamental importance to the function of the cell. If we are correct in the assumption that the primary function of the cell is to fabricate electric energy, then we may conclude that the acids produced by oxidation contribute to the production of electric energy, just as the acids and bases of a man-made battery are essential.

The mechanism within the brain-cell for the utilization of oxygen has been described by Mott as follows: [1]

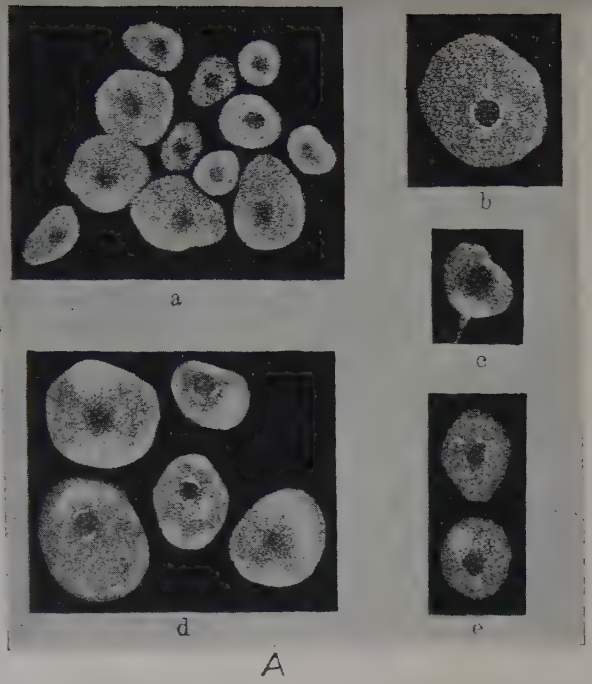
"The Nissl granules of basophile substance do not exist in the living cell. Nevertheless, the amount of this basophile staining substance in the form of Nissl granules may be regarded as evidence of the amount of energy substance (neuropotential) which the cells possessed during life. In the healthy cell it is continually undergoing disintegration and automatic reintegration. . . . If the living cell be examined by direct illumination, no Nissl bodies are seen in the cytoplasm, only fine dark granules like an emulsion. If living cells are examined microscopically with dark-ground illumination, they are seen to be filled with small granules or globules, each of which after escaping from the cell remains discrete. They are refractile and appear white and luminous; this

is due to a delicate covering film of a lipoid substance which encloses a colloidal fluid, probably consisting of a solution of salts and cell globulins. When the cell dies this colloidal fluid is coagulated and the precipitated proteid substance is massed together into little blocks—the Nissl granules; the intervening denser colloidal substance is continuous with the colloidal substance of the axon and dendron. The film that covers each granule is stainable by vital methylene blue, and a living nerve cell stained by vital blue presents the appearance of an emulsion of minute faintly blue globules. If the living cell thus stained be kept in an atmosphere of nitrogen in a warm chamber the stored oxygen is used up and a leuco-base is formed, causing the globules to lose their color, and the cells appearing of a greenish tint. On admission of oxygen the cell again becomes blue. *It thus appears possible that these granules represent a large oxygen surface, like spongy platinum, within the cell.*[1] When the cells die, the lipoidal film of the globulin-containing fluid is destroyed, coagulation occurs, and the Nissl granules are formed.

"The delicate granules filling the nerve-cells have been termed 'neuro-bions,' as if they were independent living units, but this is theory." (Fig. 14.)

The above statements suggest the theory that *the electric potential of the cells is produced by the oxidation of the lipoid films surrounding the globules* described by Mott. According to this conception, the constant supply of fats necessary to maintain these films would be supplied by the oxidation of the carbohydrates constantly brought to the cell by the blood, this oxidation being facilitated—catalyzed—by an enzyme. The oxidation of the lipoid films of the globules would in turn be facilitated by adrenalin, which is constantly supplied. As the result of the oxidation of the lipoid films acids would be produced, with a resultant increase in the hydrogen ion concentration, and an increased potential at the cell membrane. The oxidation of the lipoids would also produce a reformation of carbohydrates, an essential provision for the assurance of an uninterrupted supply of carbohydrates in the cell, since the brain has no provision for the storage of carbohydrates. Such a reverse reaction is in accord with the findings of bio-chemists; it is known to occur in plants. Such a continuous reversal of phases in the carbohydrate-

[1] *Italics ours.*



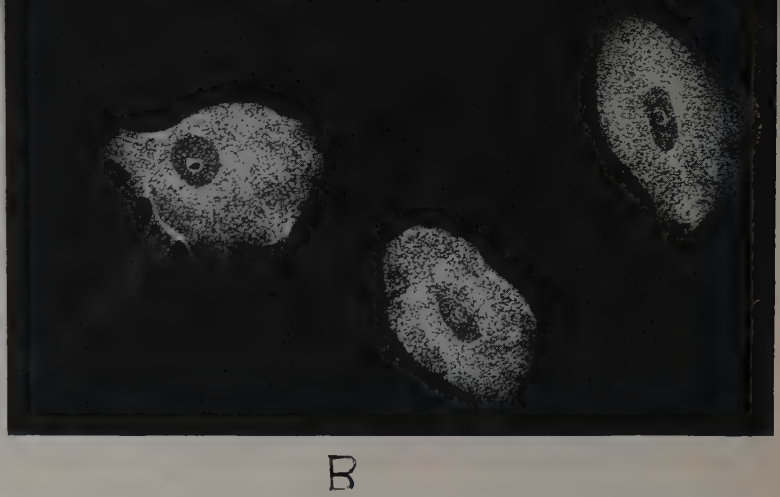


FIG. 14.—Living nerve cells as seen with the ultramicroscope.

A. Living nerve cells from the dorsal root ganglia. (a) Normal cells, from dog three days old. Fine colloidal particles in cytoplasm, showing Brownian movement. Nucleus appears nearly empty. No indication of Nissl bodies, nor of neuro-fibrils. No amœboid movement of the cell as a whole was noticed. (b) Similar cell from new-born dog. More highly magnified. Collection of particles around nucleus. (c) From ganglion in lumbar region of new-born dog. Large, brilliant granules are seen where the axone leaves. (d) Five cells from small dog. They showed spontaneous changes under observation. The brighter areas, due to larger particles, changed their positions in the cells. (e) Two cells, which had been treated with sodium iodide for eight hours. Appearance of larger aggregates of particles, surrounded by smaller ones still showing Brownian movement. (From Bayliss: Principles of General Physiology, 1920, p. 470.)

B. Drawing of an anterior horn cell (right hand) with processes and two posterior spinal ganglion cells as seen by dark-ground illumination while still in the living state. The cells are eased out of the tissue in warm cerebrospinal fluid or Ringer's fluid. The microscope is placed in a warm chamber with a glass front. In this way th eliving cells can be observed for some time. (Obj. 4 mm., apochrom. oc. 4.) (From Mott: War Neuroses and Shell Shock. 1979, p. 12.)

lipoid relation within the cells, together with the constant oxidation of the lipoid films of the globules would meet the hydrogen ion—electric potential requirements of the cell.

The intricate network formed by the dendrites of the nerve cells makes possible the linking of the cells in various combinations; and it may well be that in different parts of the

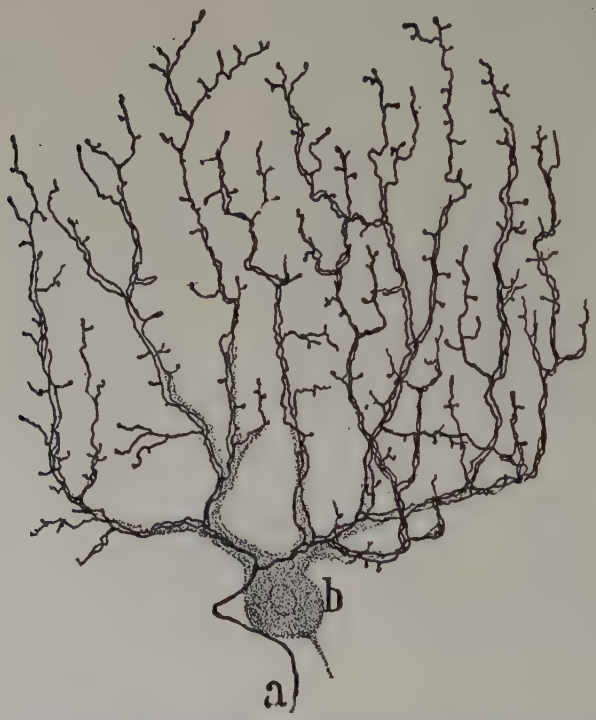


Fig. 15.—Purkinje cell with associated nerve fibres. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 1, p. 196.)

nervous system and in different organs of the body the type of communication between the cells is adapted to the nature of the specific response of that organ to stimulation. (Fig. 15.)

Whether the brain-cells are considered to be primarily condensers of the Leyden jar type or two-fluid cells, the utmost capacity value would be secured if the cells were joined in parallel, whereas the greatest electro-motive force would be

secured if the cells were joined in series. Certain observations of Cajal appear to indicate that the neurones are joined in series. (See Appendix A.) If we are correct in thus interpreting Cajal's observations this would add one more fundamental fact to the evidence which indicates that the organism is operated by electro-motive forces fabricated in and transmitted from the brain.

Reference

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CHAPTER V

A Suggested Bipolar Interpretation of the Nature of Protoplasm

Thus far we have considered cells as the fundamental units of the multicellular organism, the multicellular organism being constructed on the pattern of the single cell. It would appear, however, that in turn the bipolar pattern on which the cells are constructed must have been derived from the pattern of dynamic units in the contents of the cell. According to the bipolar theory, as we have stated, the essential characteristics of life as manifested in the cells, that is, assimilation, irritability, growth, reproduction, depend upon the presence of an electric potential which is created by oxidation. The creation of electric potential in turn requires a dielectric condenser. In the bipolar unit, the cell, we have conceived that the electric potential is produced by oxidation whereby charges are built up which are accumulated on the lipoid films—condensers—which bound the cells, the nuclei, the spherules.

If we are correct in this assumption, that the life of the component cells of the organism depends upon the creation and maintenance of an electric potential and that the various functions of life are due to variations in that potential, then within the contents of the cell—the protoplasm itself—there must also exist a mechanism for the creation of an electric potential. And if that potential is to become effective, then there must exist within the protoplasm some method of communication among the dynamic units of varying potential, as otherwise the protoplasm would be as static as the atom. In other words, if the bipolar hypothesis is to hold, we must seek to discover the essential link between the lifeless colloids on the one hand and the complex organized cell on the other; and inherent in that link must be the potentialities of the single cells of the multicellular systems. Just as the physicist has found it necessary

to support his theories of the physical characteristics of visible and tangible masses by tracing those characteristics back successively to the molecule, the atom and the electron, until now he is even attempting to analyze the electron into component parts, so any theory of life must trace the essential characteristics of life back to the most primitive form of life. Thus any theory as to the nature of protoplasm must show how oxidation can be maintained, how the functions of assimilation, of irritability, of reproduction are performed; must prevision the mechanism of memory; must show the mechanism of its own creation by means of the energy of its environment.

Let us first attempt to trace a "line of ascent" of protoplasm in terms of progressive mechanisms for the availability of energy. The atom contains large stores of energy but it is static and therefore is not available excepting under certain extraordinary conditions. In molecules the energy of the comparatively loosely held atoms is more labile and therefore is more available. In solutions the energy of the electrolytes is freely available. The interfaces of colloids provide a mechanism for the creation of an electric potential. In protoplasm, we may suppose that the interfaces between the micellæ of the colloids and the solutions in which they are suspended are more definitely constructed or fixed as monomolecular films, thus extending still further the possibility of the creation of electric potential and the availability of energy.

Every molecular or atomic disturbance in their environment must of necessity alter the potential of these differentiated micellæ or spherules, thus establishing the essential characteristic of irritability. We may consider these minute protoplasmic spherules or dynamic units to be the most primitive energy transforming units. In these infinitesimal units of energy transformation we postulate there must exist the elements which everywhere are found in the living, that is, physical structures that conduct electricity—electrolytes, and physical structures that interfere with conduction—lipoids. As long as the conditions which accumulated the original charge on the lipoid film of one of these minute masses of colloid material remain unchanged the electro-static arrangement of the ions of the lipoids would remain unchanged; and when by some for-

tuitous circumstance the environmental conditions are changed then a new electrostatic condition would be established. With the return of the original conditions we may conceive that the original electrostatic condition would return. This would be, then, the earliest and minutest suggestion of memory.

If we conceive that the lipoid films were originally formed by the electric potential created on the colloidal interfaces, this electric potential in turn promoting oxidation whereby again in turn electric potential is maintained or increased, so the infinitesimal energy transforming unit, the minute protoplasmic spherule, would in turn assemble or create new units in its own image. In accordance with this conception, this diminutive energy system, this dynamic unit of protoplasm has a bipolar structure; it has memory; it possesses the power of reproduction; it continuously creates energy; but it is in a state of dynamic equilibrium, for each of these spherules in this primitive protoplasmic mass is balanced by other spherules; it is not bipolar as a whole. It constantly creates energy but cannot utilize it effectively. As one reader of this manuscript has stated, "protoplasm is the boiler that creates the steam to be used by the engine of the cell."

Protoplasm then consists of an infinite number of infinitesimal energy transforming systems which may be called micro-micro cells and are the primitive forerunners of the multicellular organism. If this be the true nature of protoplasm, then as our methods improve, we shall be able to demonstrate the electric capacity of the protoplasmic contents of the cell just as we have demonstrated the electric capacity of the lipoid membranes of the cell. These bipolar systems of energy transformation, whether large or small, have certain common characteristics, a common method for the establishment of electric potential, a common power of oxidation, a common mechanism for constructing the building material of which they are made. By the orientation of ions as conductors with hydro-carbons as non-conductors, every conceivable variation in the degree and form of energy production is possible. Orientated molecules arranged in dynamic and in static systems constitute memory and energy, that is, they constitute respectively the machine and the driving force.

Certain investigators have claimed that minute fibers are everywhere present in protoplasmic masses. These infinitely minute fibers may well be chains of carbon molecules, as suggested by Mathews, which may be associated with electrolytic ions such as potassium to form a dynamic system. If they exist, they offer a possibility for the establishment within the protoplasm itself of infinite action patterns. The labile property of protoplasm would thus be infinitely increased and according to the forces acting upon this or upon that protoplasm, a different action pattern or system of action patterns would be established, thus making possible the infinite variety of functions which are manifested in the cells where these patterns are made effective. That is, in the primitive protoplasm the action pattern would exist but would be static; in the cell it would become dynamic. Only by presupposing such a possible differentiation of functional capacity within the protoplasm itself can the different functions of the cells of the multicellular organism be explained. Only by assuming the establishment within the primitive protoplasm of chains or systems of interrelated energy-transforming units, which register specific variations in the electric forces which produced it and which surround it, can the variations in specific response in the multicellular organism be established, or the variations in specific response be registered in the sex cells to be carried forward into new individuals, and produce "inherited characteristics."

On this basis, then, the energy units of protoplasm are miniature animals and plants; the multicellular animals and plants are enlarged complex groups of protoplasmic units.

"In this hypothesis we approach, even though only in certain respects, the most recent theories of some botanists and physiologists who . . . regard the multicellular organism not as a mere assembly or colony of cells, but rather as a simple voluminous protoplasmic body in which the nuclei are inserted at different intervals as centers or foci of energy (synergids of Sachs), and in which the membranes and other intermediate structures have produced only incomplete divisions and serve merely as supports of the organism. For example, according to Sedgewick the body of the adult animal would be only an immense syncytium whose nuclei or centers of force are dispersed throughout a single protoplasmic net work binding together the whole organism." [1]

In accordance with this conception a cell consists of a great number of ultramicroscopic cells, and again within each of the basic dynamic units, which as we believe constitute the energy transforming mechanism of protoplasm, there are probably micro-micro units, still constituted on the bipolar pattern; just as smaller than the unicellular organisms, but constructed on the same pattern, are the bacteria; and smaller than the bacteria are the bacteriophages of d'Herelle and the organisms within the so-called filtrable viruses which in the case of cancer have actually been photographed by Geye and Barnard.

It is probable that the structure of cells as revealed by the microscope represents but little of the dynamic system as it operates in the living; but the coalescences of the parts of these dynamic systems, as revealed by staining, indicate that the inner structure of the cells must be symmetrical.

Almost without exception all substances which have been investigated by the Debye-Scherrer method (X-rays) have shown a crystalline structure or at least a pattern arrangement similar to the pattern arrangement of crystals. This has been seen even in the micellæ of colloids. In accordance with these findings, we may conceive that the ultimate structure of protoplasm is probably crystalline in character, that is the dynamic units form systems of force as in crystals. The forces that produce protoplasm first produce films of water and hydrocarbons which provide the essential interfaces, where are produced the electric potentials which hold apart the ions which otherwise would coalesce into the form of crystals. Protoplasm then might be conceived to be a potential crystal, and the cell itself may be regarded as a large model of the infinitely small protoplasmic elastic crystal. The growth of a non-living crystal is along definite lines of force analogous to the lines of force along which protoplasmic growth is propagated. The components of the non-living crystal, however, are water tight, inelastic, there are no semi-permeable interfaces where electric charges can be built up. In the non-living crystal, therefore, the lines of force are static, and the crystal grows by accretion but cannot reproduce itself; in the living crystal the lines of force are dynamic, and the crystal grows by reproduction.

In support of this hypothesis as to the nature of protoplasm,

the following possible interpretations and applications of the theory may be cited:—

1. It suggests a mechanism for the assimilation of energy (food).
2. It suggests a mechanism for oxidation.
3. It suggests a rôle for the potassium and other electrolytes which are universally present in protoplasm; in particular it assigns to potassium a primary rôle because of its peculiar property of being able to hold in its field other ions at a distance, though itself in chemical combination.
4. The assumed energy transforming units in protoplasm would provide a potential for the formation of lipoid films and for the construction of lines of force by a process of displacement of the potassium ions from the lipoid films, the potassium ions in turn carrying with them and arranging the lipoid molecules and other atoms in definite systems, thus forming lines of force for energy conduction.
5. The action of anesthetics on protoplasm is the same as the action of anesthetics on the higher structure of the entire animal, because the form and structure of each is identical. Anesthetics do not interfere similarly with energy systems below the level of life.
6. This conception of protoplasm shows why colloids and cells with no energy transforming power, such as the red blood cells and blood plasma, cannot reproduce themselves. They have no inner potential—hence no assimilative power.
7. Such a bipolar conception of protoplasm provides a normal step-up from colloids as it introduces no new form of energy transforming units. Protoplasm falls normally into place as the building material of the cell, just as cells are the building material of organs, and organs are building units of the whole organism. Throughout the line there is uniformity of form and an increasing looseness of bonds, giving increasing freedom of individual action, *i.e.*, adaptation—a progressively elastic bipolarism. Whereas, on the other hand, below protoplasm there is the stratum of colloids, with a more static equilibrium, with closer bonds; below the colloid, the stratum of the solutions which are still more static, still more closely

bound; below the solution, successively the compound, the molecule, the atom—the last a fixed, unchanging unit at the other end of the bipolar scale.

Such a conception of protoplasm as made up of uniform energy transforming or dynamic units, each having the power of reproduction, each exquisitely labile yet each remaining electrostatic until disturbed by the application of external energy, gives specific properties to protoplasm. It unifies the action patterns of the infinite number of primary units in protoplasm which are so freely in communication each with the others. That is, the *nervous system* of protoplasm connects up every energy unit with every other energy unit; and these ultramicroscopic systems are connected up with the larger intracellular structures, and these with the whole cell, and each cell through the intercellular protoplasmic bridges with all the cells constituting organs; and finally through the nervous system every part of the organism is connected with all other parts. And so, also, the same force, the radiant energy of the sun, which created from inanimate matter the hydrocarbons, the colloids, the primal protoplasmic mass, in turn organizes and energizes the plant and the animal.

Reference

1. Rignano. *Inheritance of Acquired Characteristics.* (Trans. by Harvey.) Chicago, 1911, p. 41.

CHAPTER VI

Certain Established Facts Regarding Various Organs and Tissues of the Body in Relation to the Function of each in a Bipolar Mechanism

The Central Nervous System

From the mass of data regarding the structure, arrangement, chemical constitution and function of the central nervous system, practically all of which would be pertinent to this discussion, the following facts are presented because of their peculiar significance.

The infinite network of nerves—wires—in every reactive part of the organism shows that the electric control of the body processes, if such a control exists at all, is an all-inclusive control.

The facts that the nerve end-plates are spread over the surface of the muscle cells and that the neurones apparently connect with the cells by surface contact (Figs. 16 and 17); that, as Cajal [1] has demonstrated, in certain cells one branch of the neurone is apparently connected with the nucleus, and the other with the cell body (Figs. 18 and 19), thus making possible the linking of the cells in series; and that the intercommunications of the cells themselves and the end organs are not continuous but are broken by synapses—keys, these facts present a complete picture of an electrical mechanism with central batteries and connecting wires, in which the synapses intervene as make-and-break mechanisms. (See Figs. 20-24.)

As evidence which may indicate the nuclear origin of the brain and central nervous system may be cited certain facts regarding the development of the central nervous system.

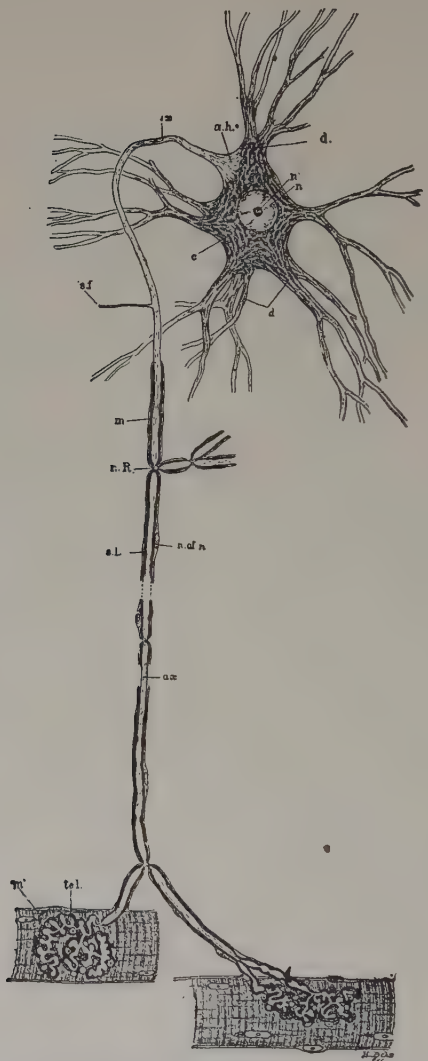

FIG. 16.—Schematic drawing of lower motor neurone. (From Barker: The Nervous System. New York, 1899, p. 898.)

(1) The ectoblast and the endoblast are separated at the first segmentation division. (Van Beneden cited by Keibel.)[2]

(2) The parts developed from the ectoblast are the epidermis and epidermic tissues, such as nails, hair and glands

of skin, *the nervous system, the external sense organs,* and the mucous membrane of the mouth and anus. The skin and the specified mucous membranes are in effect external sense organs.

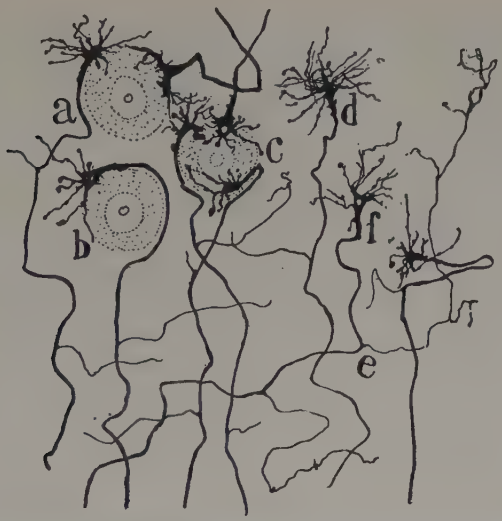

FIG. 17.—Termination of the fibres of the ascending branch of the cochlear nerve. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 1, p. 787.)

The parts developed from the ectoblast are therefore essential parts of the nervous system.

(3) According to Hubrecht [3] both in Elasmobranchs and in mammals the cellular material which is present in those very earliest stages contributes especially—as it does in the trochophora—towards the formation of the anterior part, the head, and following upon this, a proliferation process is inaugurated.

(4) Hubrecht imagines that the nerve ring on the oral disk of the actinian represents the spinal cord. In the primitive streak "we encounter the material which also in the Actinia—(1) proliferates downwards from the ectoderm and produces the stomaderm; (2) coalesces with the entoderm; (3) is in direct continuity with those parts which are preparing to give rise to coelomic pouches, but are not yet continuous with the primitive enteron."

(5) The above facts would appear to indicate that the ectoblast, which produces the central nervous system, may be the principal source of the energy whereby is effected the further subdivision into the tissues derived from the endoblast, and into the mesoblast and its organs and tissues.

(6) The anlage of the nervous system is differentiated

Fig. 18.—Drawing of longitudinal section of a spinal ganglion. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 1, p. 131.)

very early in development. In the earliest embryo in Mall's list, the brain portion of the medullary canal is already marked off and shows beginning segmentation. Child [4] has shown that in the embryo the brain leads all other structures in growth and development, and like the bud of the plant has the highest metabolism. His and Keibel have indicated the significance of the order of development of the various organs and tissues.

(7) The power of the nervous system to create new cells is indicated by certain functions of the nucleus which have

been demonstrated by Pfeffer.[5] In Pfeffer's experiments the nervous system of multicellular organisms appears to have been shown in miniature, and his observations offer such convincing evidence in support of the conception of the nuclear

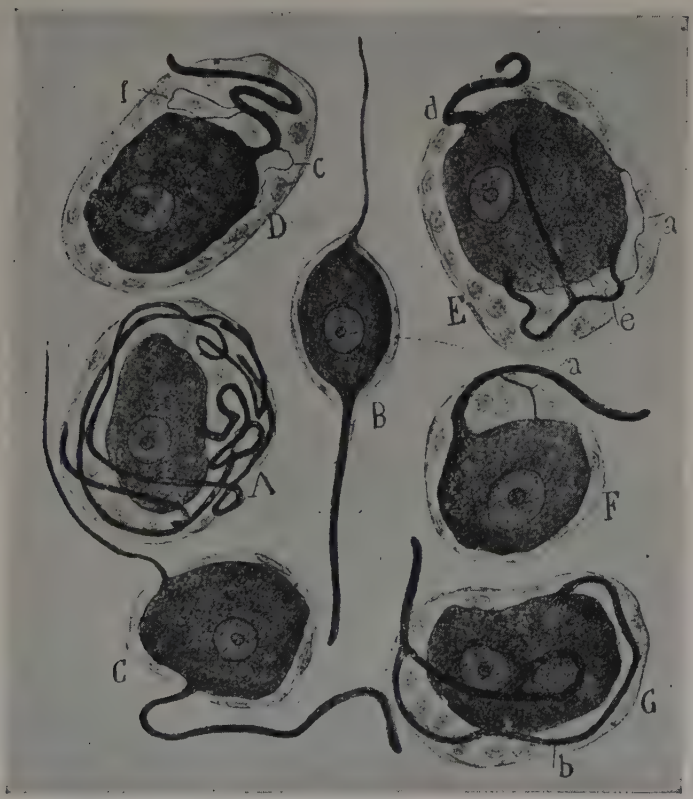

Fig. 19.—Different forms of cells in the plexiform ganglion of the vagus nerve. Note in G the apparent association of one of the nerve fibres with the nucleus and of the other with the cytoplasm of the ganglion cell. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 1, p. 440.)

origin and function of the central nervous system, that it has seemed well to include here the following extensive quotation:

"After having detached by plasmolysis the cell membrane of the nucleated protoplasmic body of a plant cell, and dividing the cell

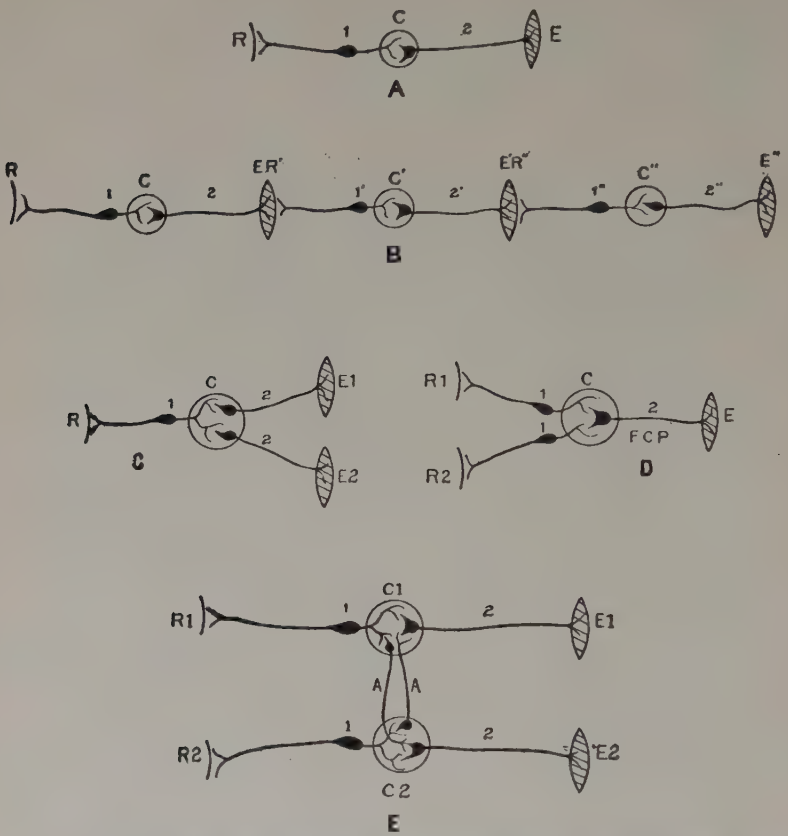

FIG. 20.—Diagrammatic drawings illustrating five types of reflex arcs. (From Herrick: Introduction to Neurology. Philadelphia, 1918. p. 61.)

in halves, one containing a nucleus and one without any, he observed that only the nucleated half had surrounded itself with a new cell membrane. If, however, the part deprived of a nucleus remained united to the nucleated fragment even by only a very fine protoplasmic filament, it also was capable of secreting its little cellulose membrane.

"Pfeffer varied his experiment also in the following manner. He prepared cells of a moss protonema in such a way that an entirely isolated, anucleate mass of protoplasm remained united to the neighboring cell which contained a nucleus by means of thin filaments piercing the cell wall. In this case a membrane was

formed round the anucleate fragment. But the membrane was not formed if the neighboring cell had been itself deprived of its nucleus.

"In the formation of this cellular membrane in anucleated parts of the cytoplasm united by protoplasmic filaments with other nucleated portions, the maximum intervening distance observed by Pfeffer was 3.7 mm. 'But the nucleus can certainly exercise the membrane forming stimulus at an even greater distance.' If

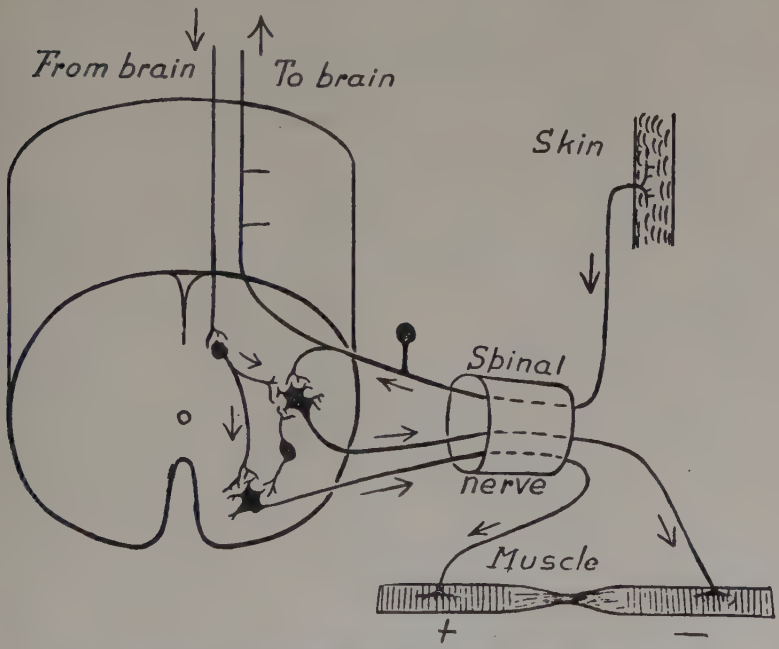

Fig. 21.—Diagram of simplest possible spinal reflex mechanism. (From Johnstone: Mechanism of Life. London, 1921, p. 117.)

the nucleus remains united with a whole chain of anucleated bits of cytoplasm 'the production of the membrane appears to advance centrifugally and so to commence a little later in the more remote portions of cytoplasm, than in the bits nearer the nucleus.'

"From these experiments one is inclined to think, this author concludes, 'that the production of a cellular membrane required the continuous transmission and coöperation of certain states of motion and vibration which radiate out from cell nuclei or rather owe their origin to the reciprocal action of nucleus and cytoplasm.'

"Oscar Hertwig makes in this connection the following remark: 'This experiment proves that the stimulus necessary for membrane formation can be transmitted by thin connecting filaments which traverse the septum interposed between two cells. Nothing hinders us then from assuming that some similar transmission goes on in other functional conditions.'

"But it is very probable that this nervous current or discharge

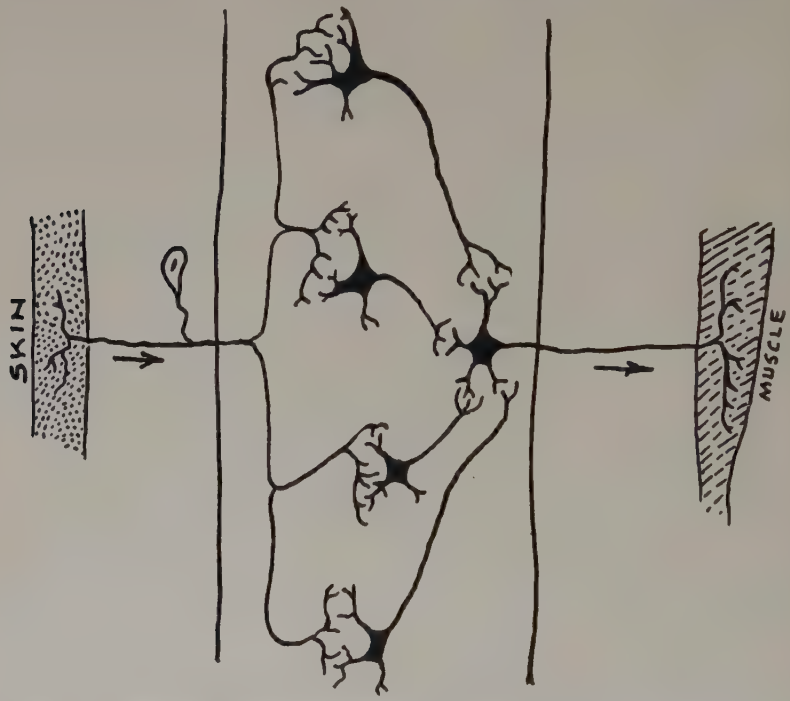

FIG. 22.—Diagram illustrating method of reinforcement of afferent nerve impulse (after Herrick).

which is conducted from the nucleated cell along the protoplasmic filaments to the anucleated fragment of the contiguous cell, also passes across into the fragment even when it contains a nucleus and so also when it is replaced by an entire cell. This leads us to the conception that wherever intercellular protoplasmic connections are present, the various nuclear currents of discharges stream through these connections and so permit a general nervous flux throughout the whole network of these protoplasmic bridges, in

the meshes of which the nuclei themselves would constitute the nodal points. In this way one would have a continuous circulation or distribution of nervous energy throughout the entire organism.

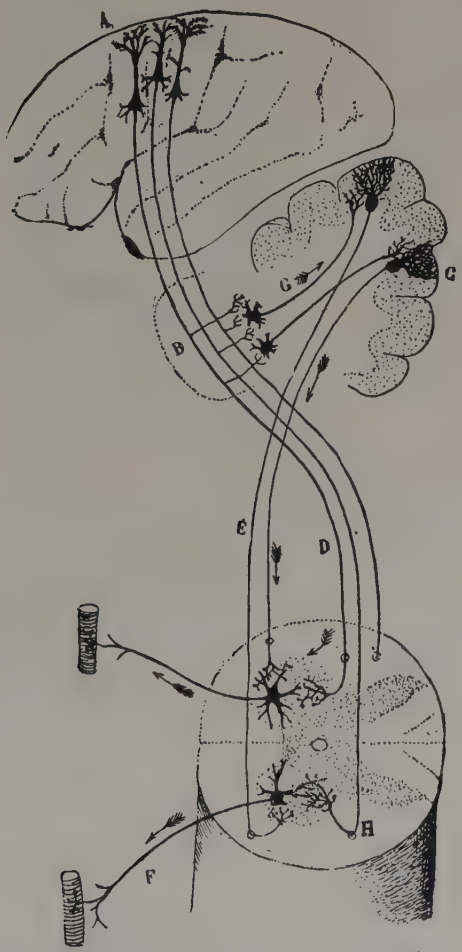

FIG. 23.—Schematic drawing of complete sensory-motor circuit. (From Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 1, p. 547.)

"The augmentation of the nervous system in these ways will have as its result an augmentation of the trophic stimulus which it exercises; so that the cells situated along these ways will grow and proliferate more rapidly, thus producing a zone characterized by

numerous mitoses. The augmentation of the vital processes of these cells will in consequence of increased osmotic attraction, attract a greater quantity of nutritive fluid, exactly as the wick of

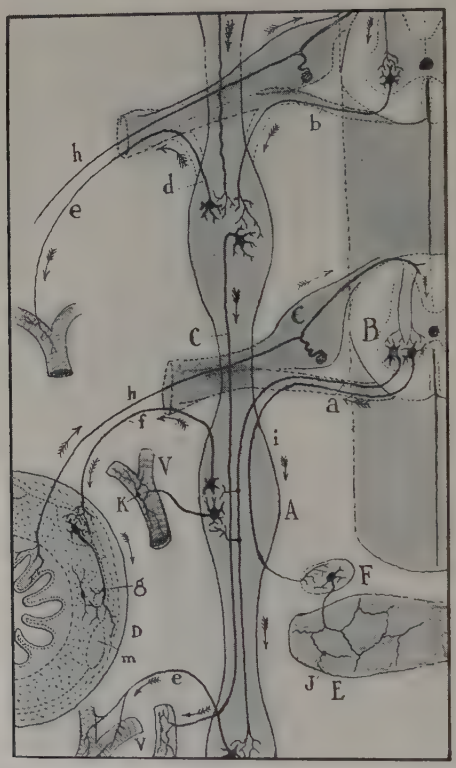

Fig. 24.—Schematic drawing of the sensitive and motor paths in the sympathetic nervous system. (Redrawn from Cajal: Histologie du Système Nerveux. Paris, 1911. Vol. 2, p. 941.)

a lamp which is stimulated by a current of air draws up by capillarity a larger quantity of combustible fluid."

(8) In support of this view may be cited also the findings of Kofoid and his collaborators in their studies of the neuromotor apparatus of certain intestinal parasites in which the primitive apparatus of flagella and the protoplasmic areas from which they originate appear to be of a truly nervous

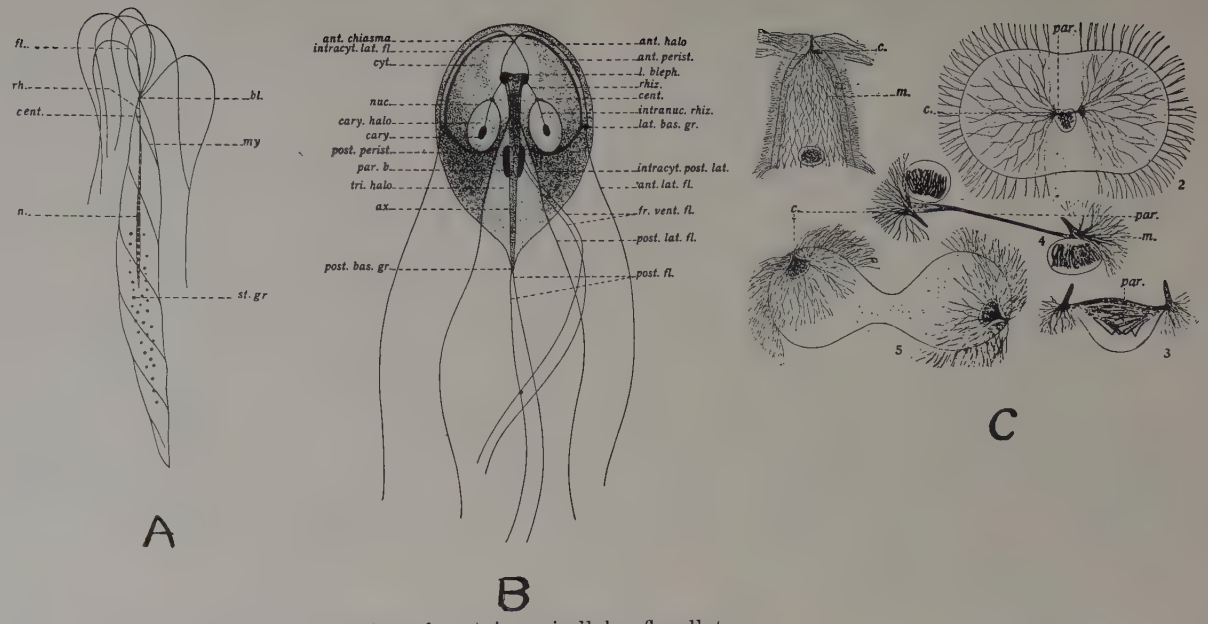

FIG. 25.—The neuro-motor apparatus of certain unicellular flagellates.

A. Streblomastix Strix. (From Kofoid and Swezy: On Streblomastix Strix, a polymastigote flagellate with a linear plasmodial phase. Univ. Calif. Publ. Zool., 1919, Vol. 20, pp. 1-20.)

B. Giardia Muris. (From Kofoid and Christiansen: On Binary and multiple fission in Giardia Muris. Univ. Calif. Publ. Zoöl., 1915, Vol. 16, pp. 30-54.)

C. Trichonympha. (From Kofoid and Swezy: Flagellate affinities of Trichonympha. Proc. Nat. Acad. Sci., 1919, Vol. 5, pp. 9-16.)

Note in each the nuclear relations of the flagellates.

character and to be dependent upon the nucleus both for origin and for function.[5] (Figs. 25 and 26.)

"The close physical connection between the blepharoplasts at the base of the flagella and the nucleus, the metabolic center of the cell, throughout the period of flagellar activity, is indicative of the intimate relation which the nucleus bears to these energy-expending structures. It cannot be merely the physical tug of the moving flagella which pulls the nucleus to its anterior position, for the blepharoplasts retain this anterior location when the nucleus moves posteriorly, the connection between them being retained merely by the slender nuclear rhizoplast. The rounding-up process in the cytoplasm of the encysting individual doubtless exerts some pressure leading to spatial readjustments, but the translation of the nucleus appears to be out of proportion to this single factor. *In the active phase of the organism the nucleus is nearest to the center of metabolic activity,*[1] and in the passive phase of encystment it tends to assume a place as near as possible to the center of the cytoplasmic mass, the cytostomal pouch appearing to hold it off from the fully central location."

There is a striking analogy in the above description to the findings of Magini (cited by Cajal)[6] who in studies of the cerebro-electric lobe of the torpedo observed that in periods of rest the nucleolus occupied a central or slightly eccentric position in the nucleus, while in periods of activity it moved in the direction of the axon to the membrane of the nucleus where it came in contact with the point of origin of the cylinder axis, with the resultant development of the nervous (electric) wave which discharged the electric organ. (Fig. 27.)

All of these facts and the conjectures suggested thereby would indicate that throughout phylogeny nerve tissue like the nucleus has been an energy-producing tissue; and that the central nervous system may justly be considered *the direct descendant of the nucleus of the original unicellular organism.*

Since in a bipolar mechanism, the electric current must flow from areas of higher to areas of lower potential, it is necessary to cite such facts as may tend to support the conception that the cells of the brain are the principal source of the electric energy that coördinates the body and to show how the direction of the fabricated current is established.

[1] *Italics ours.*

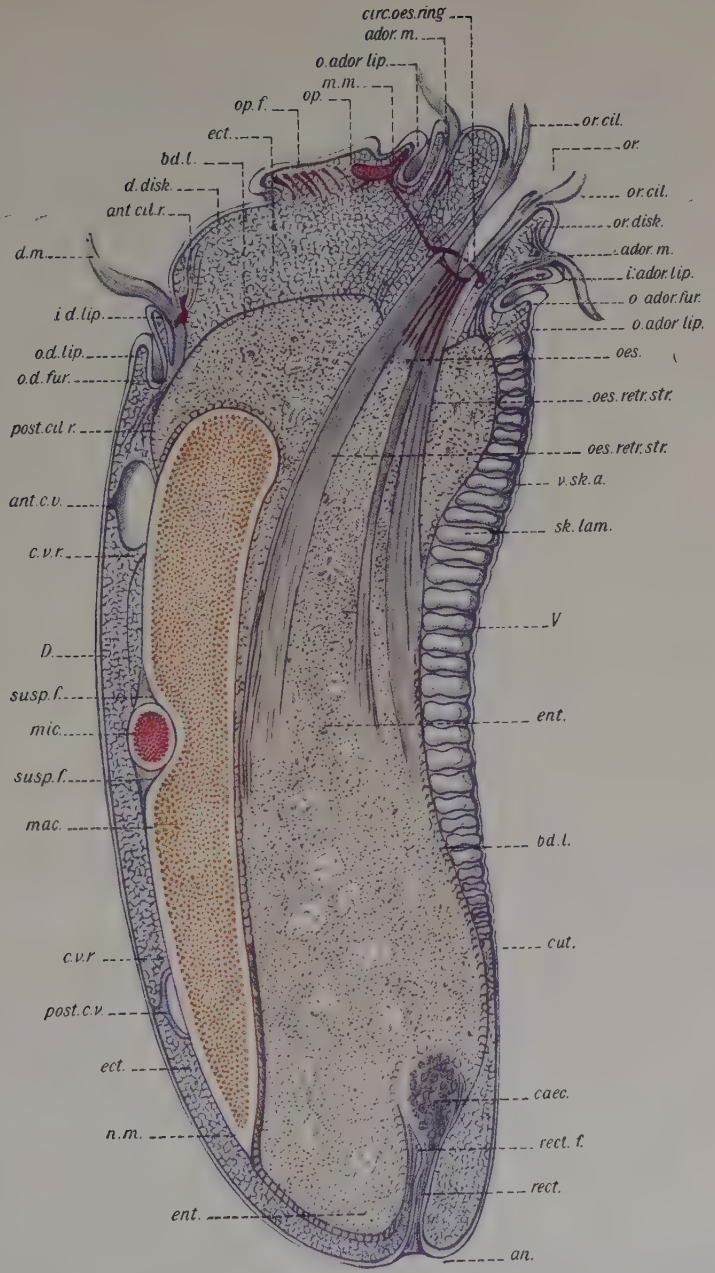

FIG. 26.—The neuro-motor apparatus of Diplodinium Ecuadatum. Note the identical staining of micronucleus (mic) and of the neuromotor fibres communicating with the membranelles and cilia and of the motorium (m.m.). This organism is a striking example of a high degree of differentiation in a unicellular organism. (From Sharp: *Diplodinium Ecuadatum* with an account of its neuromotor apparatus. Univ. Calif. Publ. Zoöl. 1919, Vol. 13, pp. 43-122.)

Since according to experimental findings the low-conducting extremely thin lipoid films which surround the cell body and the nucleus have a high electric capacity, it would seem that the potential within the cells must be very high as compared with the potential within the axons which are surrounded by

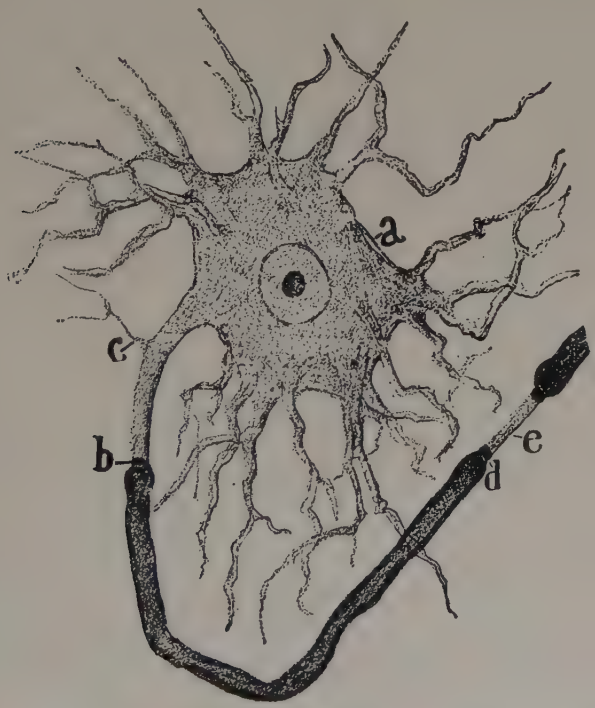

FIG. 27.—Cell from the cerebro-electric lobe of a torpedo. (From Cajal: Histologie du Système Nerveux. Paris, 1911, Vol. 1, p. 152.)

a thicker myelin sheath. The electric current, therefore, would pass from the highest potential within the cells through the zones of lower potential in the axons and nerves toward the points of lowest potential in the glands and muscles to be stimulated. In accordance with this conception, when the "wave" of potential in its passage from the cell through the axon reached a certain "pressure" the synapse would become sufficiently polarized to allow the current to pass across it to

the structures beyond. Thus the synapse may be in effect a projected part of the lipoid film surrounding the nucleus and the cell; and being endowed with less resistance to the passage of electric charges, after a certain pressure is reached, the current would break through.

Clinically the control of the body by the energy fabricated in the brain, which we believe to be electric energy, is indicated by the result of high division of the spinal cord; by the result of the paralysis of the motor end-plates by curare; by the result of the suspension of the activity of the higher brain centers by inhalation anesthesia; by the result of breaking the nerve connection with any part; by the fact that when the supply of oxygen is cut off no energy is created and equilibrium or death follows. Any disabling influence whereby either the connection of the brain with a part of the body is broken or the function of the brain is disabled or lost renders the body helpless.

The brain cannot work continuously, but a reversible process is necessary at regular intervals to restore it. This process in the higher centers is called sleep. The more intense the activation, the more needed is sleep. The brain is the only organ that sleeps conspicuously. Of great significance is the fact that the entire man spends one-third of his time waiting for the brain to restore itself, or, according to the bipolar theory, to put itself again in the position of being able adaptively to transform potential into kinetic energy in the form of electricity, which in turn drives the body.

The Liver

If the brain and central nervous system represent the nucleus of the original unicellular organism, that is, the part of highest metabolism, the highest degree of positivity, then some other organ or tissue must be its antithesis—must be the center of negativity. That the liver primarily represents certain essential functions of the cytoplasm is suggested by many facts, among which the following are of especial significance:

1. The cytoplasm of the unicellular organism receives and stores food; the liver receives and stores food (glycogen).

2. The cytoplasm of the single cell picks up and has an affinity for the acid by-products produced in the nucleus and in the cytoplasm itself; in the higher animals the liver plays a similar rôle.

3. The nerve cells, like the nuclei of unicellular organisms, possess no neutral fat, no glucose, no acid-neutralizing material; these are stored in the liver for the benefit of the brain as well as for itself and for other organs and tissues.

4. In the amœba neither the cytoplasm nor the nucleus can function without the other; in the higher animal the brain cannot function without the liver; the organism cannot function without the brain. The brain and the liver work simultaneously; the brain and the liver are restored simultaneously.

5. The early evolutional appearance of the liver is significant. Although the function of the so-called hepatic cells of the polyps has been disputed, nevertheless the gradual concentration and development of these cells from the polyps through the echinoderms, annelids, insects, etc., to the fishes, reptiles, birds and mammals, make it appear that the peculiar functions of the cytoplasm which we have described above began to be assigned to specifically differentiated cells (liver) at a very early period in evolution.

6. In the embryo the anlage of the liver appears in the very earliest stages of development, *being practically coincident with the appearance of the anlagen of the central nervous system.* The embryonic development of the liver is exceedingly rapid, the organ almost filling the abdominal cavity in the third month, when its weight is approximately 10.5 per cent of the entire body weight, and throughout life its weight is usually about 2 per cent of the entire body weight. As Keibel and others have stated, the precocious appearance of the anlagen of certain organs *is undoubtedly associated with the necessity for their early development,* the anlagen mutually influencing each other in the development of the organism as a whole.

In addition to these facts, which would appear to suggest the cytoplasmic origin and function of the liver, many facts may be cited, which indicate not only the interdependence of the brain and the liver, but also their antithetic rôles in the or-

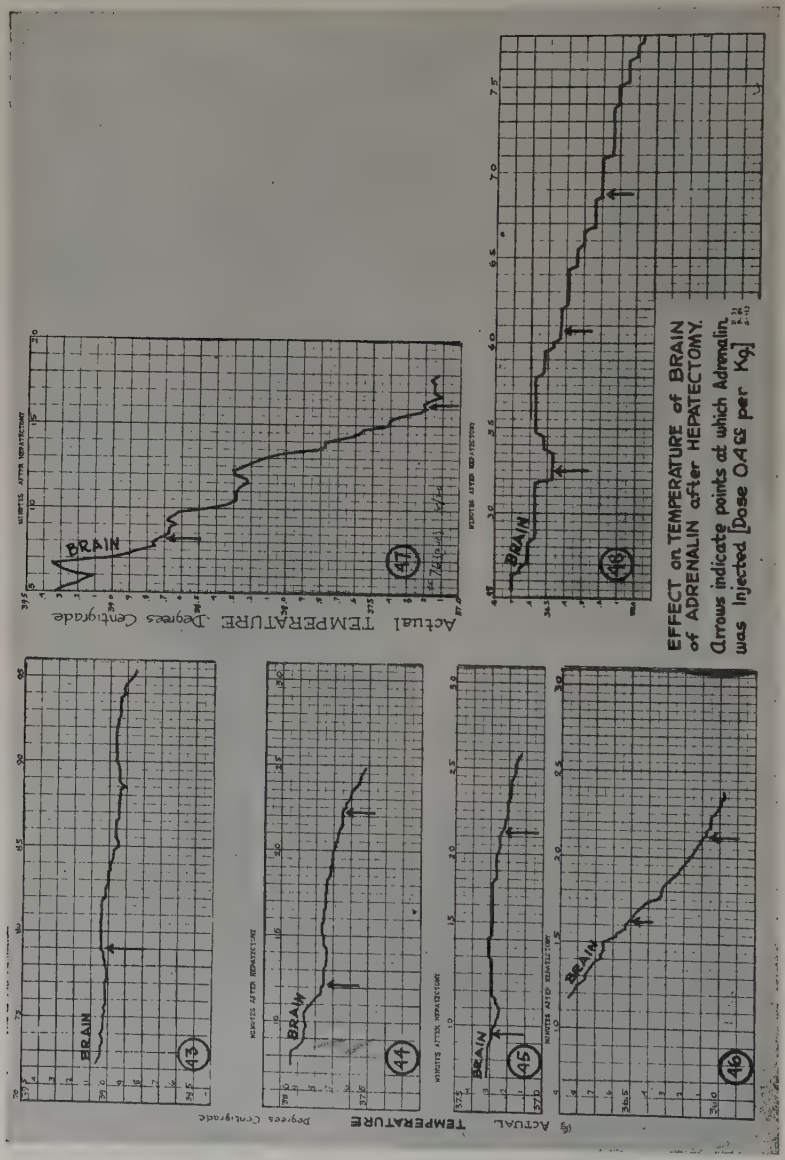
EFFECT on TEMPERATURE of BRAIN
of ADRENALIN after HEPATECTOMY.
Arrows indicate points at which Adrenalin
was injected [Dose 0.4cc per Kg.]
BRAIN
Actual TEMPERATURE Degrees Centigrade
MINUTES AFTER HEPATECTOMY

FIG. 28.—Temperature charts showing lack of response in the brain to the injection of adrenalin after hepatectomy.

ganism. These facts indicate also that this interdependence is due to some relationship which is not explained by any current theory. How, for example, can we account for the progressive changes in the brain and the inevitable death after the liver is excised; or for the alteration in the functioning of the brain when the liver is damaged? (Fig. 28.) These changes are not due to a want of glycogen, for the administration of glycogen does not prevent death. It does not seem that death after hepatectomy can be due alone to the loss of the power of the liver to split up acid by-products for the following reasons: (1) Life is not prolonged by the administration of large doses of morphin for the purpose of minimizing metabolism and in consequence diminishing the amount of acid by-products; (2) the repeated transfusion of blood does not prolong life; (3) the administration of acid-neutralizing alkalies is of no avail. It would seem that the dramatic fall in body temperature might be an important factor in the inevitable death which follows excision of the liver; but the maintenance of the normal temperature by artificial means does not prevent death. No therapeutic measure has been found of avail in acute yellow atrophy of the liver or after the excision of the liver.

In addition to the fact that death is the inevitable result of excision of the liver, there are certain other outstanding facts which cannot be interpreted by any conception of the method of operation of the organism which has thus far been proposed. Among these the following are of especial significance:

1. When the adrenals are removed the liver cells with the brain cells undergo a physical disintegration. Neither the brain nor the liver can survive without the adrenals. (Fig. 29, C and F.)
2. After decapitation, if the adrenals remain intact, the liver cells do not break down.
3. The injection of adrenalin increases the stainability of the brain cells and the liver cells. (Fig. 29, B and E.)
4. The liver and the brain, and to a lesser degree the adrenals, are affected simultaneously by any cause of exhaus-

tion. These organs work and are exhausted simultaneously; they are restored simultaneously.

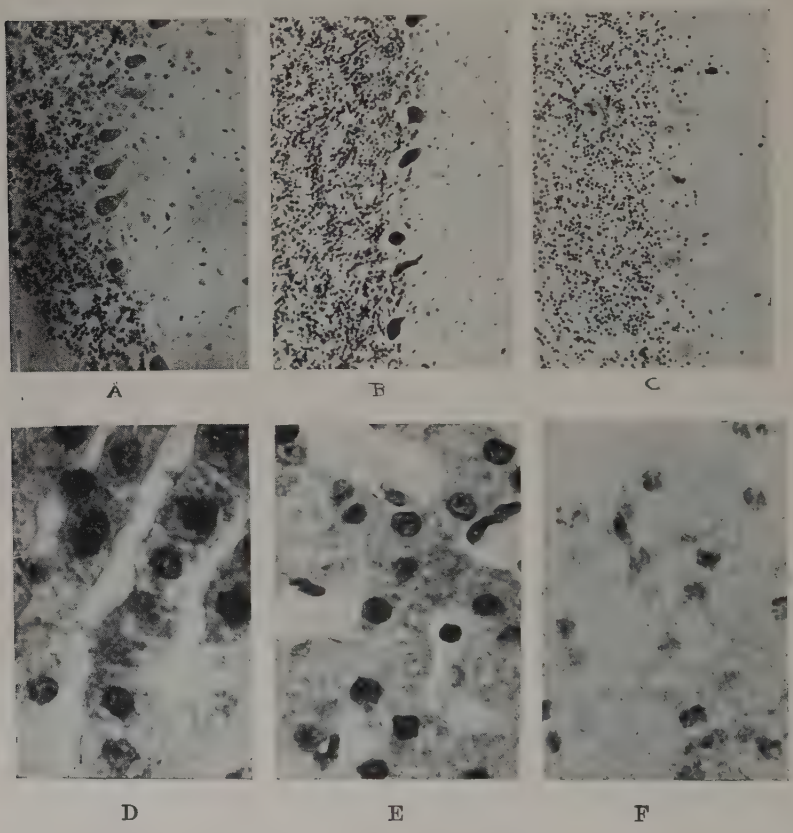

FIG. 29.—Effect of the injection of adrenalin and of adrenalectomy on the cells of the brain and of the liver. A. Section of cerebellum of normal dog. B. Section of cerebellum of dog after injection of adrenalin. C. Section of cerebellum of dog after adrenalectomy. (From photomicrographs × 310.) D. Liver of normal dog. E. Liver of dog after injection of adrenalin. F. Liver of dog after adrenalectomy. (From photomicrographs × 1640.) Note the hyperchromatism of the Purkinje cells in B as compared with the chromatolysis in C; and the vacuolation and disappearance of nuclei in F as compared with E.

5. Want of oxygen causes loss of brain function and death. Want of liver function causes loss of brain function and death. These facts suggest that nerve cells require for their

action the presence of oxygen, of adrenal function and of some rôle played by the liver.

6. In every experimental test the liver has been found to be exceedingly sensitive to change, even more so than the brain. This was shown in resuscitation experiments; in perfusion experiments; by observations of its unequalled rapidity of autolysis; and by measurements of its electric conductivity.

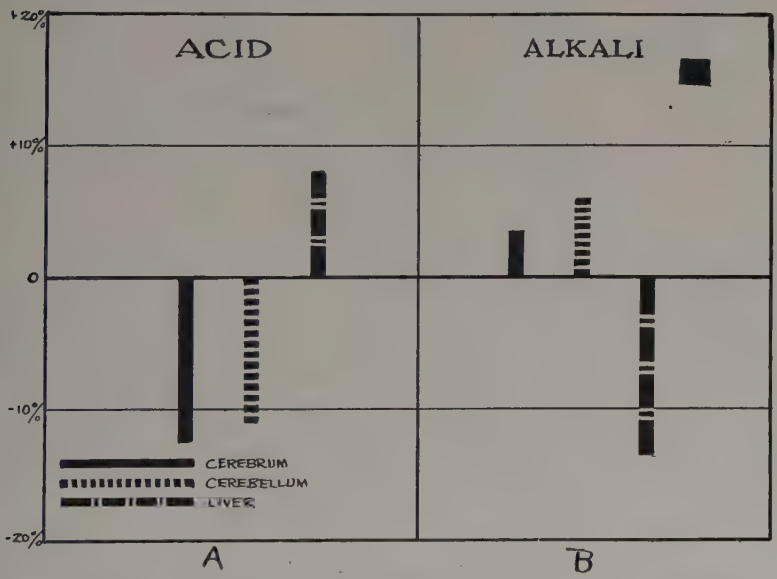

FIG. 30.—Opposite effects of the injection of (A) an acid and (B) an alkali on the electric conductivity of the brain and the liver.

7. In studies by Renauld-Capart he noted that "the first fact established was that the abdominal blood is essential to the function of the brain centers. This being demonstrated we directed our research to discover which of the abdominal organs could so affect the blood as to influence the cerebral activity. We have from the very first established that the blood which passes through the liver has the property of reëstablishing cerebral functions; following this, that the liver alone, of all the abdominal organs, has that property." [7]

8. The chemical constitution of the liver is in harmony with the conception that it is the negative pole of a bipolar

organism. The liver is rich in mineral substances—potassium, sodium, phosphoric acid, chlorin, iron and alkaline earths. The tendency of the liver cells to accumulate mineral sub-

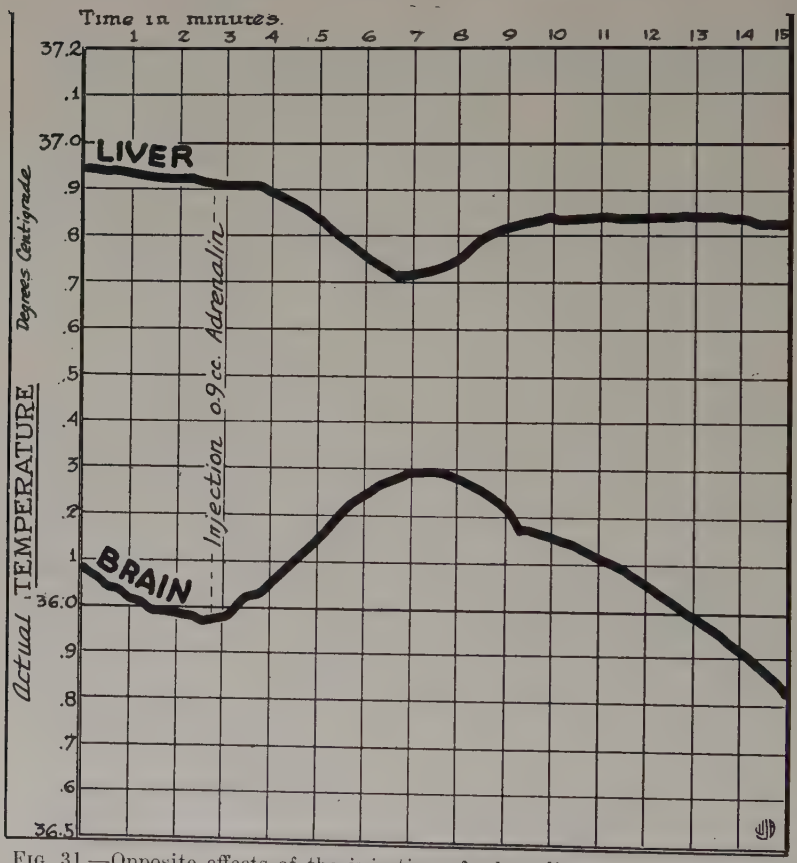

FIG. 31.—Opposite effects of the injection of adrenalin on the temperature of the brain and of the liver.

stances, especially metals, has been emphasized by Roger. (See Appendix A, p. 237.) On the other hand, the metallic content of the brain is exceedingly minute as compared with the liver.

Finally, and of prime importance, are the biophysical findings that the application of any stimulus causes opposite changes in the conductivity of the brain and the liver. Thus,

in the stage of stimulation by any agent, the conductivity of the *brain* is *increased;* the conductivity of the *liver* is *decreased.* In the stage of exhaustion, the conductivity of the *brain* is *decreased;* the conductivity of the *liver* is *increased.* (Fig. 30. See also Fig. 4.) In like manner, the temperature changes in the brain and the liver tend in opposite directions. (Fig. 31.)

This evidence shows the interdependence of the brain and the liver, and suggests that while the brain cells are purely oxidizing mechanisms, the liver, which is the only organ in the body supplied with venous blood, is in effect an earthy solution, certainly negative, and therefore a most suitable medium for "grounding" electric currents.

The Activating Mechanisms

In our conception of man and animals as bipolar mechanisms we assume that the brain is a passive mechanism, and that, like man-made machines, it can act only in response to some form of stimulation, which, in the animal mechanism, may be either internal or external stimulation such as light, or sound, or taste, or chemical or electrolytic change, or the suggestion of any of these by sounds or symbols. These stimuli are constantly applied. All the activities of daily life demand that the brain respond constantly to them, while in periods of stress, an increased response is demanded.

It follows, therefore, that there must be one or more activating organs, the action of which can be applied as needed to the regulation of the response of the brain to stimulation. Variation in the activity of the brain itself implies variation in oxidation. Variation in the speed of the work done by the electricity fabricated in the brain implies variation in the passage of the electricity from the brain to the effector organs and tissues.

Oxidation is markedly controlled by adrenalin. The electric conductivity of living tissues is increased by iodin. The adrenal glands produce adrenalin; the thyroid gland hoards and metabolizes iodin into an iodin-bearing hormone. It would seem, therefore, that to these two organs, the adrenals and the thyroid gland, may be assigned the rôle of *activators.*

The Adrenal Glands

The adrenal glands are activators and that their aid is promptly elicited when increased metabolism—increased work—is required, is suggested by the fact that adrenalin alone produces nearly all the symptoms produced by the various causes of increased energy-transformation, such as emotion,

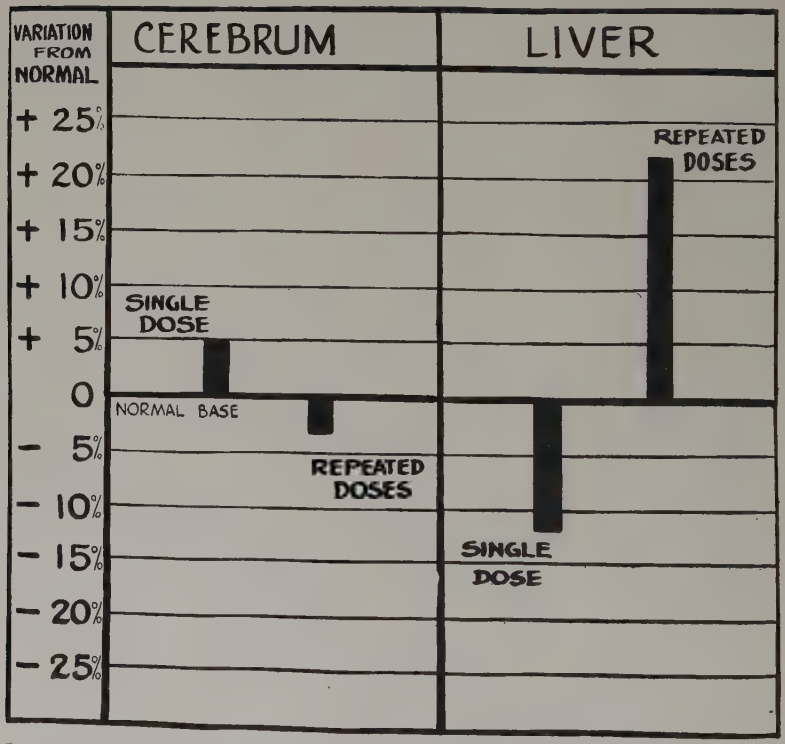

Fig. 32.—Immediate and late effects of the injection of adrenalin on the electric conductivity of the brain and the liver.

exertion, injury, infection. That is, adrenalin causes increased metabolism, increased thyroid activity, increased blood pressure, increased pulse, increased respiration, leucocytosis, increased sweating, dilation of the pupils, diversion of the blood to the surface, lowering of the threshold at the myoneural junction.

Of no less significance are the facts that adrenalin causes hyperchromatism and later chromatolysis of the brain cells just as do emotion, injury, exertion, infection; that it causes an immediate increase in the electric conductivity of the brain (Fig. 32); that it increases the temperature of the brain (Fig. 33); and that when the adrenals are removed, the brain cells rapidly degenerate, the animal rapidly loses the power to fabricate heat, and muscular and mental action; and death usually follows. We conclude, therefore, that the

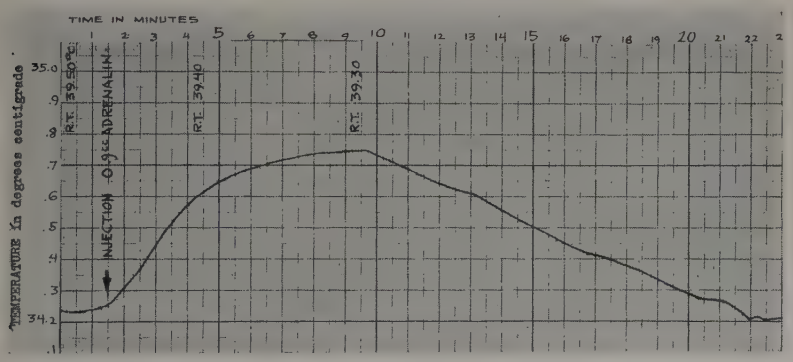

Fig. 33.—Effect of the injection of adrenalin on the temperature of the brain.

brain is dependent on the adrenals, both for function and for survival.

Our studies of electric conductivity showed that adrenalin first increases the conductivity of the brain, as in the inceptive stage of shock, and that the conductivity is then decreased, as in other forms of stimulation. If conductivity is related to stimulation, then an increase or decrease in conductivity would be associated with an increase or decrease in function, i.e., with activity or exhaustion. Our electric conductivity observations have indicated that in the inceptive stage of shock or exhaustion the conductivity of the brain is increased, while in every type of exhaustion studied, the conductivity of the brain was decreased when the state of exhaustion was established.

If the activation of the brain is a phenomenon of electric

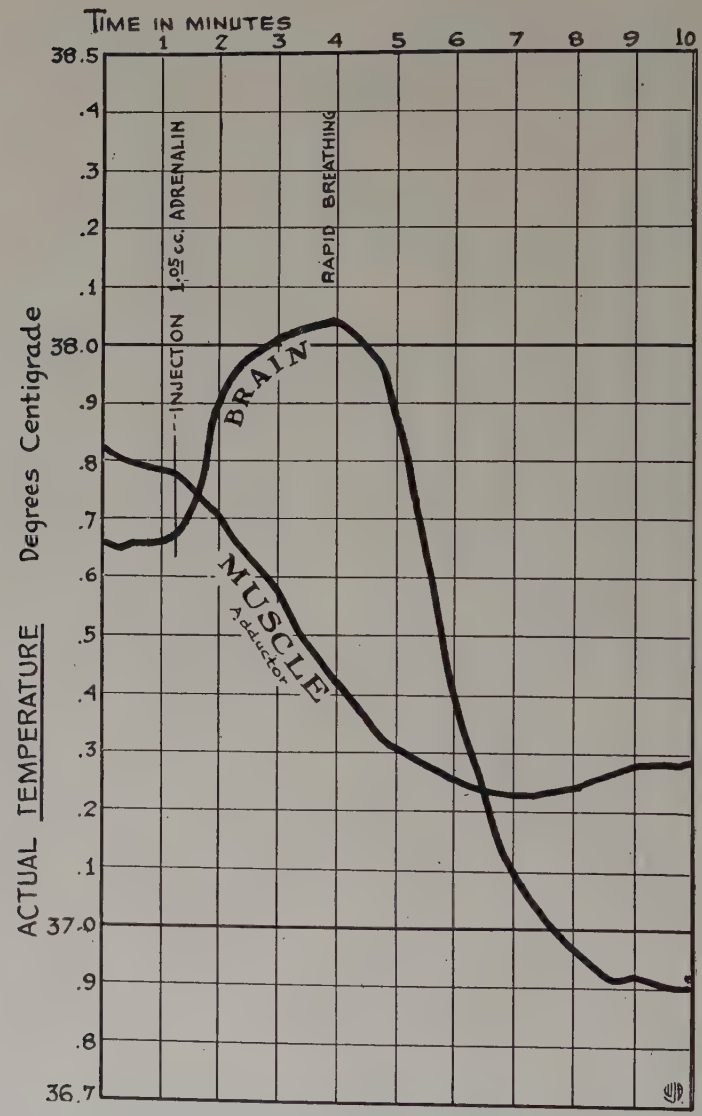

FIG. 34.—Opposite effects of the injection of adrenalin on the temperature of the brain and of voluntary muscle.

energy, then since electric energy depends upon oxidation, and oxidation in part at least is controlled by adrenalin, it

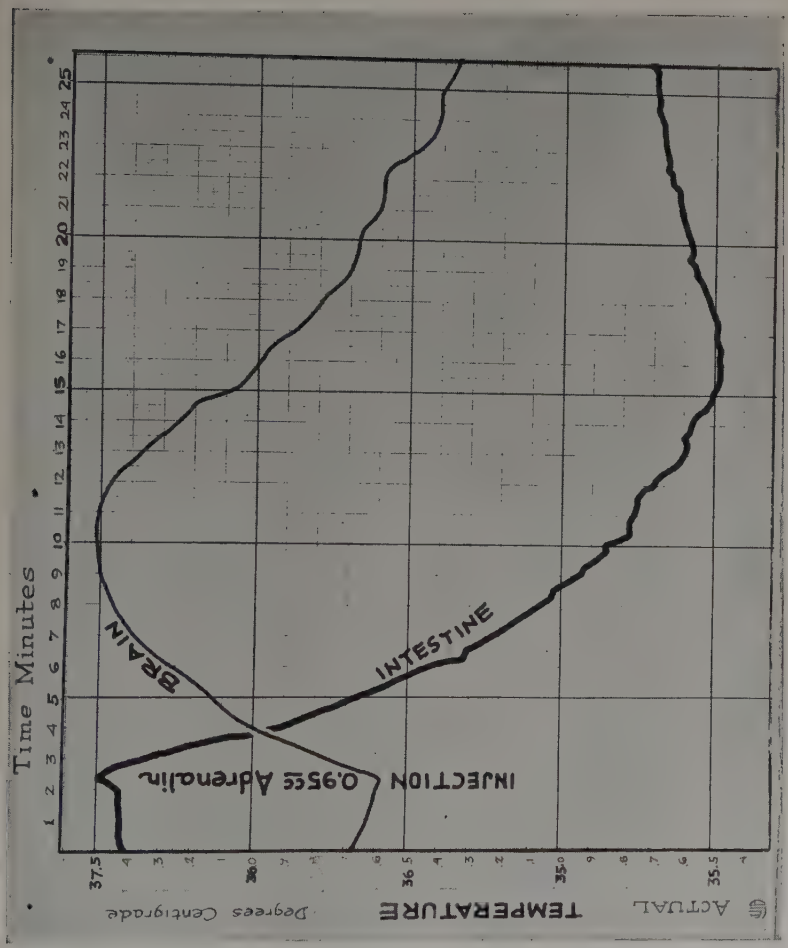

FIG. 35.—Opposite effects of the injection of adrenalin on the temperature of the brain and of the intestinal mucosa.

follows that excessive adrenalin would ultimately cause fatigue and decreased permeability. If oxidation is in part controlled by adrenalin, then the injection of adrenalin would increase oxidation and it should be possible to measure that increased oxidation by temperature variations. Our temperature studies have shown an increased temperature in the brain after the injection of adrenalin; but—and this is of prime significance—after the injection of adrenalin the temperature of most of the other organs and tissues was unchanged or diminished. (Figs. 31, 34 and 35.)

The experimental and clinical phenomena thus far placed in evidence when harmonized by the bipolar theory, seem to indicate that living organisms are driven by electricity, which is fabricated in the brain cells with the aid of adrenalin. But we have seen no evidence that the effects of adrenalin cover more than the emergencies of moments and hours, or at the most, of days. The action of adrenalin is too evanescent to maintain evenly an increased receptivity, increased sensitiveness, for weeks and months. We assume that the brain has no power within itself to do this, and that, therefore, prolonged activation of the organism must be accomplished through the aid of some other organ.

The Thyroid Gland

The need of the organism for iodin is marked by the development of the thyroid gland as a single compact body coincidently with the emergence of animal life from the sea. Doubtless the lower marine animals in which the specialized gland is lacking secured sufficient iodin directly from the iodized sea-water. In the fishes and cyclostomes the thyroid is represented only by small groups of cells hardly as large as pinheads scattered along the larger blood vessels near the heart and along the gills. The gland begins to become more compact in the amphibians, and develops progressively through the various stages of land animals until it reaches its highest development in man. The speeding of the metamorphosis of the tadpole by thyroid feeding has been repeatedly demonstrated. The need of iodin in the marine animals, also, has

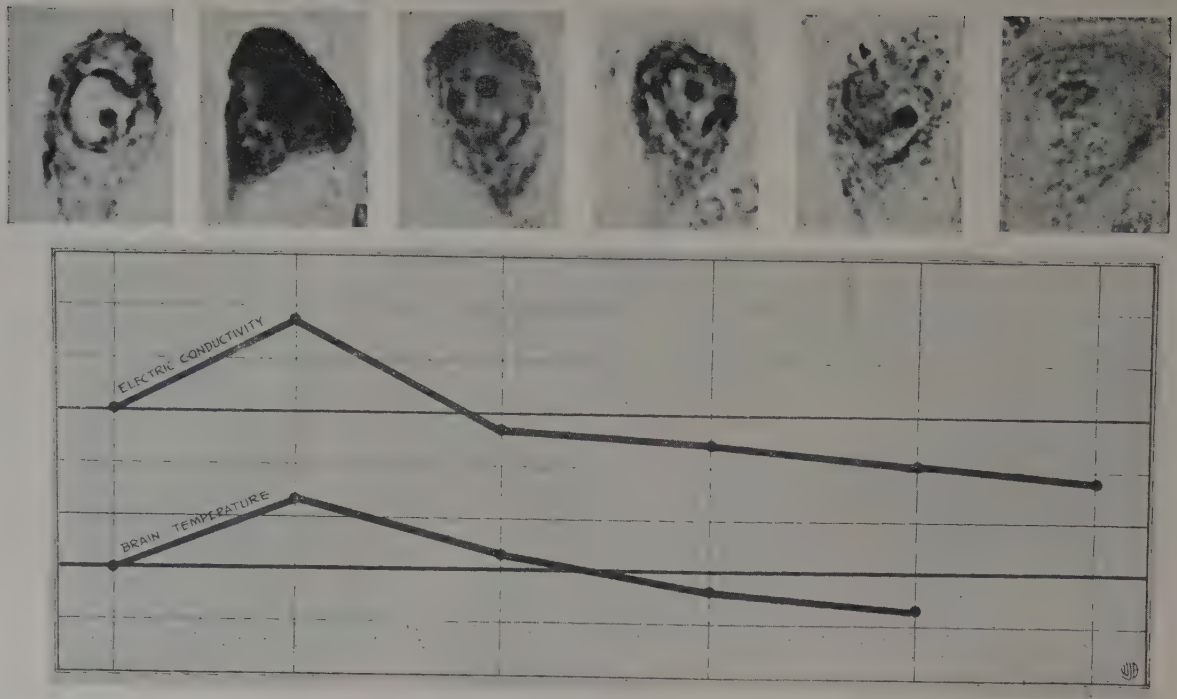

FIG. 36.—The similarity of the progressive effects of the injection of adrenalin on the structure, the electric conductivity and the temperature of the brain. A. Photomicrographs of sections of the cerebellum from animals killed at varying intervals after the injection of adrenalin. The conductivity and temperature measurements also were made at progressive intervals after the injection of adrenalin.

been strikingly demonstrated by the development of enlarged thyroid bodies in fishes kept in inland tanks, the water in which contained no trace of iodin. Marine [8] and his collaborators conclusively linked up the function of the thyroid with the demand of the organism for iodin when they wiped out the occurrence of goiter in the trout of the Pennsylvania State Hatcheries by adding iodin to the water.

Clinically, it is well known that iodoform poisoning causes symptoms identical with those of an acute infection. In our laboratory we found that iodoform produced brain cell changes identical with those produced by exertion, emotion, infection, physical trauma, etc. When the secretion of the thyroid is abnormally increased as in hyperthyroidism, the whole organism becomes exquisitely sensitized, and the body functions are dramatically displayed, projecting as it were a magnified physiologic picture. Iodism alone duplicates the symptoms of hyperthyroidism.

In those chronic diseases or conditions in which an increased metabolism has continued for a considerable period of time, as, for example, in tuberculosis, in chronic infection, in the rutting season, in pregnancy, in hyperthyroidism, there is frequently a hyperplasia of the thyroid gland. Each of these states is characterized by increased metabolism, increased pulse, unstable heart action—excitation with consequent fatigue.

The relation of the function of the thyroid to periods of prolonged stress is strikingly illustrated by the fact that in the lowest vertebrates and in certain of the lower vertebrates the groups of thyroid cells are connected with the ducts of the sexual organs. In the lower forms of life practically the only occasion for protracted activation beyond the needs of the moment is in connection with procreation. This direct connection persists as far as the cyclostomes. The relation, however, continues to be evidenced in the higher mammals by the enlargement of the gland in periods of sexual stress—sexual excitement, menstruation, adolescence, pregnancy.

In our biophysical laboratory we found that the electric conductivity of the tissues was increased alike by the administration of iodin and of thyroid extract. (Figs. 37 and 38.) Of particular significance was our finding that the injection of

adrenalin into an iodized animal produced an abrupt rise in the temperature of the brain, the amount of which far exceeded that observed in normal animals. (Fig. 39.) The manner in which iodin acts as an activating agent by controlling the phe-

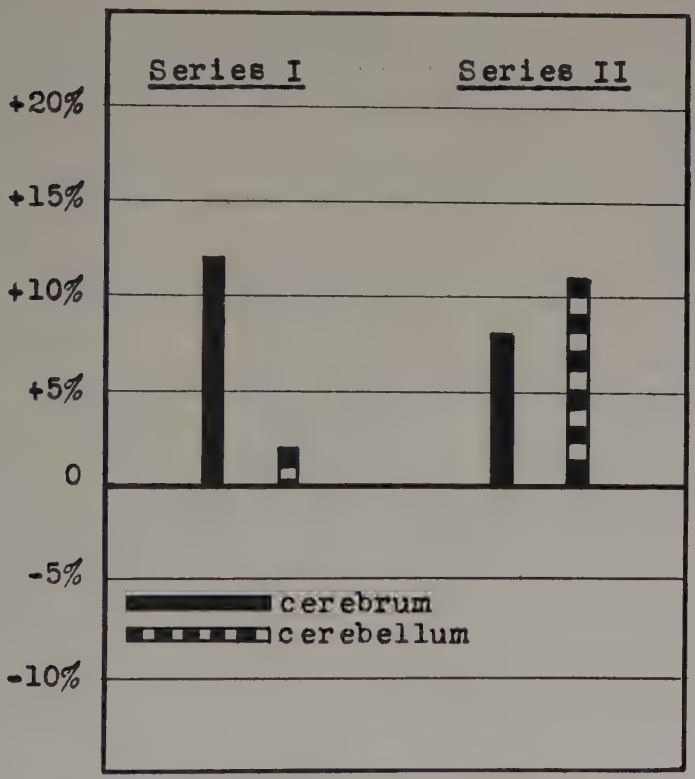

FIG. 37.—Effect of the absorption of iodin (iodoform) on the electric conductivity of the brain.

nomena of oxidation is suggested by the conclusions of Moureu and Dufraisse from their studies of the "catalytic properties of iodin and its compounds." [9] From previous studies they had concluded that "iodin and its compounds play catalytic rôles in the phenomena of autoxidation and that in particular under certain conditions they should possess an anti-oxidizing property." They found that at certain concentrations compounds

of iodin had an autoxidizing action, at other concentrations an anti-oxidizing action; and that with free iodin also a retardation of oxidation preceded the acceleration of oxidation, the protraction of the former depending upon the concentration of the iodin in the solution used.

"In the presence of the findings which we have presented it is in order to ask what may be the rôle of iodin in nature.

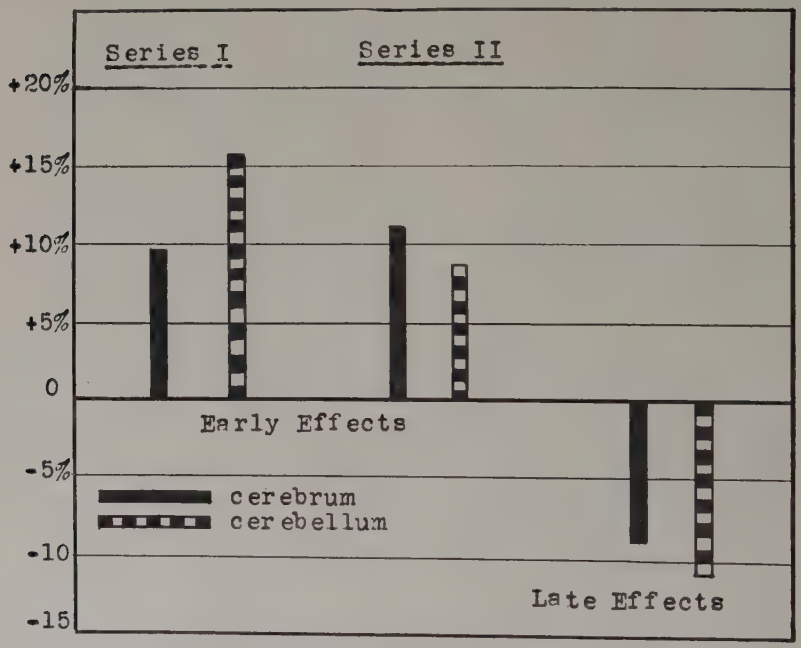

Fig. 38.—Early and late effects of thyroid feeding on the electric conductivity of the brain.

"Let us state at first that it is largely distributed throughout the mineral kingdom. It is present in notable proportions in the fundamental sphere of iodin, where live innumerable beings which often assimulate the metalloid in their organs. One finds it, moreover, in all living beings, vegetable or animal, and it is ordinarily ranked among those essential to life. (A. Gauthier, Baumann, Grey.)

"According to our researches, might we not suppose that in most cases, iodin acts as an agent for the regulation of the phenomena

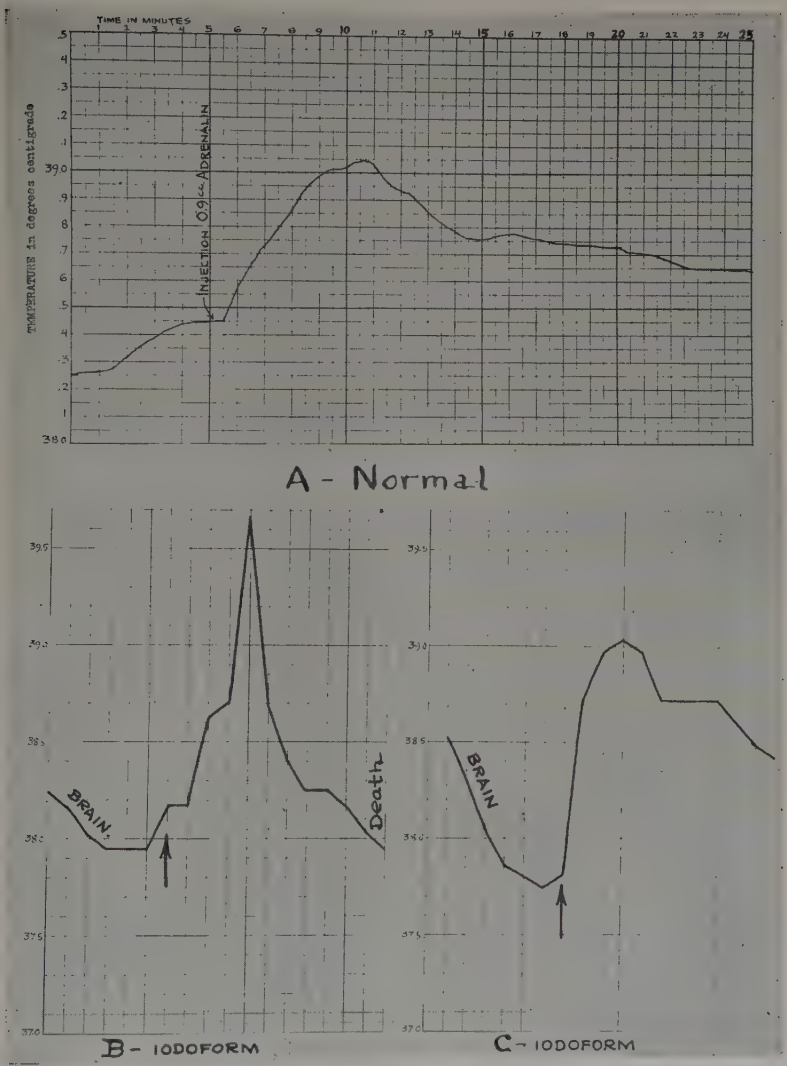

FIG. 39.—Comparative effects of the injection of adrenalin in normal and in iodized animals. Note the extreme and abrupt changes in the temperature of the brain in B and C as compared with the normal response to the injection of adrenalin in A.

of oxidation? But feeble quantities of energy suffice to make iodin pass from the state of a positive catalyzer to that of a negative catalyzer, or inversely, according to the needs of the organism.

"Following this line of thought, one cannot but be struck by the fact that the superior animals, especially those that live in a medium very poor in iodin, concentrate this element in an organ to which is attributed definitely the rôle of a regulator of oxidation —the thyroid gland."

One further distinction should be drawn between the function of the adrenals and of the thyroid in their rôle as activating glands. It has been shown that without the adrenals the nerve cells rapidly degenerate, and death follows. Without the thyroid life may persist, but as a vegetative process only. The power of response to stimulation is lacking; the power of the organism to do work is negligible. Only sufficient electricity is generated for the essential life processes. If, however, as Kendall has dramatically demonstrated, the specific iodized product of the thyroid gland be administered to such an individual, the sensitization of the organism is inaugurated at once, response to stimulation is made possible and power to do work is established.

The Blood and Lymph

The one essential rôle of the blood in a bipolar mechanism would seem at first thought to be only that of an oxygen carrier, of a medium of exchange between the nerve cells and the organs and tissues which supply the elements essential to their activity.

In a bipolar mechanism, however, such as we conceive the animal organism to be, not only must the principal circuit between the points of highest and of lowest potential be maintained, but a complete electric communication between all the constituent cells of each organ and tissue throughout the circuit must be no less surely established. Such an assured intercommunication would be established by means of a fluid of high conductivity, and of neutral reaction. These essential characteristics are supplied by the blood and by the lymph, derived from the blood, by which every cell is surrounded—a medium more negative than the cytoplasm of the cells of the various organs.

In this sense, we might conceive of the blood as cytoplasm in solution, by means of which there is established a common cytoplasmic fluid connection between the liver and the brain and central nervous system, assuring the complete reciprocal functioning of these two "poles" of the bipolar mechanism. Thus we would conceive of an animal as a syncytial structure.

Thus the blood would accomplish for the nervous system what the fluids of the cytoplasm of the amœba do for the nucleus—serve as the means of electric communication. In higher animals an elaborate system of nerves has been evolved to meet this need in part, but it would appear that the cytoplasmic fluid has persisted also.

This is but an extension, or adaptation to the bipolar theory of the suggestion by Wooldridge. (Mathews.)[10]

"The blood as a whole, including the endothelial cells of the blood vessels, may be considered to be living matter, distinguished from most other living matter by its greater fluidity. There are, however, other kinds of living matter of a liquid kind. The protoplasm of the amœba and many plant cells is so liquid that it flows readily and is in reality a circulating liquid. The blood plasma may be regarded as a very liquid protoplasm formed essentially by the cells of the vascular endothelium, by the blood cells and the hematoblasts. The blood platelets and the red blood corpuscles may be regarded, from this point of view, as homologous with the granular inclusions of many cells. Blood separated from the endothelial cells dies and clots; in just the same way a peripheral nerve dies if severed from its nutritive center. We shall in this chapter adopt this point of view of Wooldridge and consider the whole blood, the more liquid portions together with the corpuscles both white and red, the platelets, and the cells lining the blood vessels, as consisting of a great mass of living protoplasm. The processes which occur in the blood are then in many important particulars probably identical with those occurring in living matter generally. . . . The alkalinity of the blood is about the same as that of the tissues generally and the methods of maintaining its alkalinity are those employed by all forms of living matter. A study of the alkalinity of the blood, its variation both physiological and pathological and the means employed to hold it constant, throws light on the alkalinity of every cell."

The Muscles

Many established facts regarding the phenomena of muscular activity are in accord with the bipolar theory.

Electric stimulation of the controlling nerve supply of the various voluntary muscles and of the various glands of the body makes these muscles and these glands do what the brain makes them do.

Stimulation of the motor area of the cortex of the brain causes muscular activity resembling everyday voluntary activities, such as closing the hand, bending the wrist, the elbow, the ankle, the knee, chewing, turning the head, turning the eyes, puckering the lips, increasing the respiration, etc. We have already cited (p. 38) the observations of Gotch and Horsley.

The severing of the nerve connection between the brain and a muscle leads not only to paralysis, but to atrophy of the muscle; but if the muscle be made to contract at certain intervals by electric stimulation, no atrophy of the muscle follows. Electricity does for the muscle, as far as its function and nutrition are concerned, what the brain does for it. Therefore, electricity is adapted to the muscle and the muscle is adapted to electricity.

That muscles belong to the "cytoplasmic" division of the animal mechanism is suggested by their comparative alkalinity; by the fact that unlike the nerve cells but in common with the other hypothetical cytoplasmic organs and tissues they store glycogen, proteins and fats, which may be utilized by the nerve cells as well; "In times of fasting or starvation the muscle protein is torn to pieces and converted into amino-acids, which, passing from the muscle to the blood, are carried by that internal medium to those organs of which the metabolism is keener, to the brain and nervous tissues and the heart, and serve to nourish these organs at the expense of the muscles." (Mathews.)[11]

Like the liver, so the muscles are to some degree dependent upon the adrenals. "Impulses impinging on the suprarenal glands cause these to set free substances which profoundly effect the metabolism of the muscle." (Mathews.)[12]

Not only has the stimulating nerve current to the muscle been demonstrated to be an electric current, but in the response itself electricity or heat or both are generated.

The activity of muscle depends upon oxidation and is related to variations in the H-ion concentration.

According to A. V. Hill "considerable electro-motive forces are produced by the activity of excited muscles or nerves—up to three or four hundredths of a volt." [13]

Hill has shown further that in a muscle the heating effect produced by the electric change accompanying a nervous impulse is not more than one hundred thousandth part of the energy liberated in a twitch. On the other hand, as he states, the electric change is sufficient to stimulate other tissues. The possibility that the nuclei of the muscle cells play an essential rôle in the phenomena of muscular action is suggested by Mathews: "A very interesting but entirely unsolved problem is the possible involvement of the nucleus in the processes of contraction and energy metabolism." [14] That the muscle cells possess an electric potential is suggested by their acid-alkali variations in periods of activity and rest, and by the elaborate mechanisms for the neutralization of the acids which are formed during work. It would appear then that the nervous impulse to a muscle is the catalyzing agent which "fires" the energy stored in the muscle cell itself and thus initiates the complex chemical changes—in themselves electrical phenomena, which produce the phenomena—motion or heat—of muscular activity.

The Organism as a Whole

In accordance with our general conception we may suppose that in the original unicellular mechanism, each reaction, each response to environment was an electrical response between the nucleus and the entire cell body, the essential potential being accumulated on the nuclear membrane. At a very early stage in the life of this first protozoan, however, variations in the chemical constitution of different portions of the cytoplasm must have established varying potentials within these portions and thus determined the direction of the electric current. For example, one may readily suppose that at the point at which

ingested food was received the immediate resultant changes in electrolytic concentration at that point would determine the direction of at least a portion of the electric current. It is not our purpose, even if it were possible, to consider the various steps by which from the primary differentiation of the parts of the early unicellular organism the highly differentiated multicellular organism was developed. Nor does space permit a discussion of the possible specific function of other parts and tissues than those most immediately concerned with the fabrication and release of the electrical energy which operates the bipolar mechanism.

We believe that many generally accepted facts could be marshalled whereby we might interpret in bipolar terms not only the function of the effector organs—muscles; of the essential activating organs—the thyroid and the adrenals; but also of the heart and circulatory system, which are essential for the conveyance of the secretions of the essential activating organs to the nerve cells; of the pituitary gland with its possible function of conserving the essential alkaline balance—the formula of the sea—within the organism by its regulation of the salt content of the cells and its further function of regulating skeletal growth; of the digestive system with its selective power of supplying the essential constituents of the cells.

It is sufficient to our purpose here to emphasize the fact that it would seem that each organ and tissue of the body but fulfills a rôle previsioned in the functions of the cytoplasm and nucleoplasm of the original simple unicellular bipolar mechanism.

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CHAPTER VII

A Suggested Bipolar Interpretation of Certain Clinical Phenomena

The Synaptic System

As has been emphasized in a previous chapter the neurones are nowhere in direct physical contact with each other and the lines of communication between the neurones and the muscles, glands, etc., are broken by synapses.

The synapse, as suggested by Sherrington, may be endowed with special properties: "It might restrain diffusion, bank up osmotic pressure, restrict the movement of ions, accumulate electric charges, support a double electric layer, alter in shape and surface tension with changes in difference in potential, alter in difference of potential with changes in surface tension or in shape, or intervene as a membrane between dilute solutions of electrolytes of different concentration or colloidal suspensions with different sign of charge." [1]

The synapse then may be regarded as a highly adapted switch which now closes the circuit, now opens it; now diminishes the current, now accelerates it.

An electric current flows from an area of a higher to an area of lower potential, hence the electric battery—the nerve cell—would be in constant action, excepting for the intervention of the synaptic switch. If the nerve cell and the end-organ were constantly connected, then the nerve cell would be in the position of the battery of a door-bell whose button is pegged. With the living electric circuit closed at the synapse, the nerve cell would work continually and would be exhausted just as certainly as the electric battery in a closed circuit becomes exhausted. And to the same extent the stimulated organ—the gland cell, or the muscle cell—would be worn by continuous stimulation.

The presence of a synapse as a mechanism of adaptive electric connection and disconnection is as important as the spring which breaks the electric current of the door-bell when the pressure is released. Conversely, the presence of the synapse supports the conception that there is an electric potential in

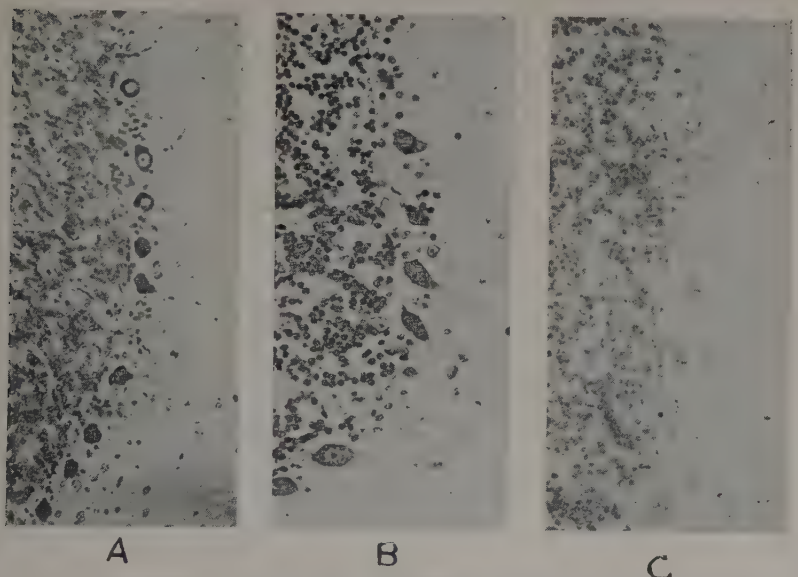

Fig. 40.—Early (B) and late (C) effects of strychnin poisoning on the brain cells. Compare the hyperchromatism in B and the chromatolysis in C with the appearance of the normal brain cells in A. (From photomicrographs × 310.)

the living neurones; that the nerve cells act in some such manner as do accumulators.

Strychnin Poisoning

In view of this conception, the phenomena of strychnin poisoning suggest that strychnin may act on the synapses in such a way that the electric circuits of many cells are closed at once, so that there results the universal and violent stimulation of muscles which constitutes a convulsion. Moreover, not only the muscles, but other mechanisms are stimulated also, as

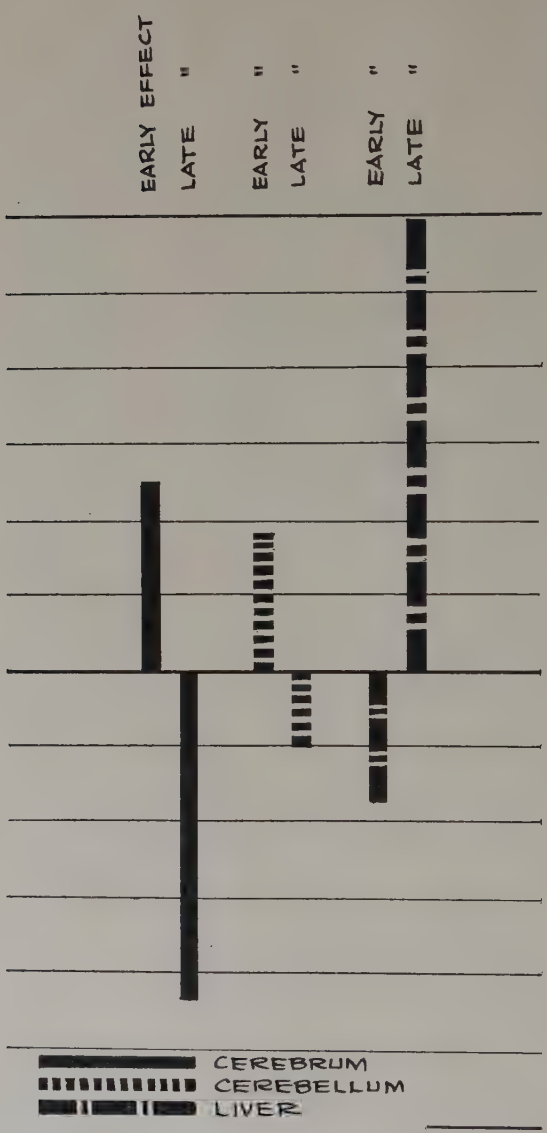

FIG. 41.—Early and late effects of strychnin poisoning on the electric conductivity of the brain and of the liver.

is evidenced by an increased output of adrenalin; a marked increase in blood-pressure; and a complete cycle of changes in the brain cells, first a stage of hyperchromatism, then a stage of chromatolysis, and finally, in some cells, swelling, rupture of the nuclear and the cell membranes, and final death of the cells. (Fig. 40.) These changes in the brain cells are paralleled by changes in the electric conductivity of the brain—first an increased conductivity followed by a decrease which is in direct relation to the degree of exhaustion. (Fig. 41.) During the period of stimulation the oxidative capacity of the brain varies in direct relation to the clinical effects. (Fig. 42.)

Tetanus

We may assume that the stimulus from tetanus toxin, which is known to pass up the axis cylinder, passes along the axis cylinders of the nerve fibers until it reaches the synaptic junction, and closes the circuit, thus causing a contraction. It would appear that closing the circuit at the synapse "pegs the bell," so that a vast muscular area becomes in effect one pole of a great battery, the other pole being the brain, and the nerves the connecting wires, the circuit of which is closed by the action of the tetanus toxin.

The Bio-Electrical Reorganization of Disabled Organs and Tissues

If physiologic activity is the equivalent of electric stimulation, then electricity is apparently the means by which cells are organized, for, as Mathews points out, if the eyelids of puppies be kept closed, the related brain cells will not be developed.[2] If the nerve supply to muscles is cut off, the muscle cells become disorganized; but electricity will reorganize them. When limbs are fractured or soft parts injured, voluntary exercise best reorganizes the muscles and nerve cells from the disorganization of disuse. Children who are not allowed to play do not develop strongly; that is to say, their muscles are not organized by the electric energy of exercise. If groups of

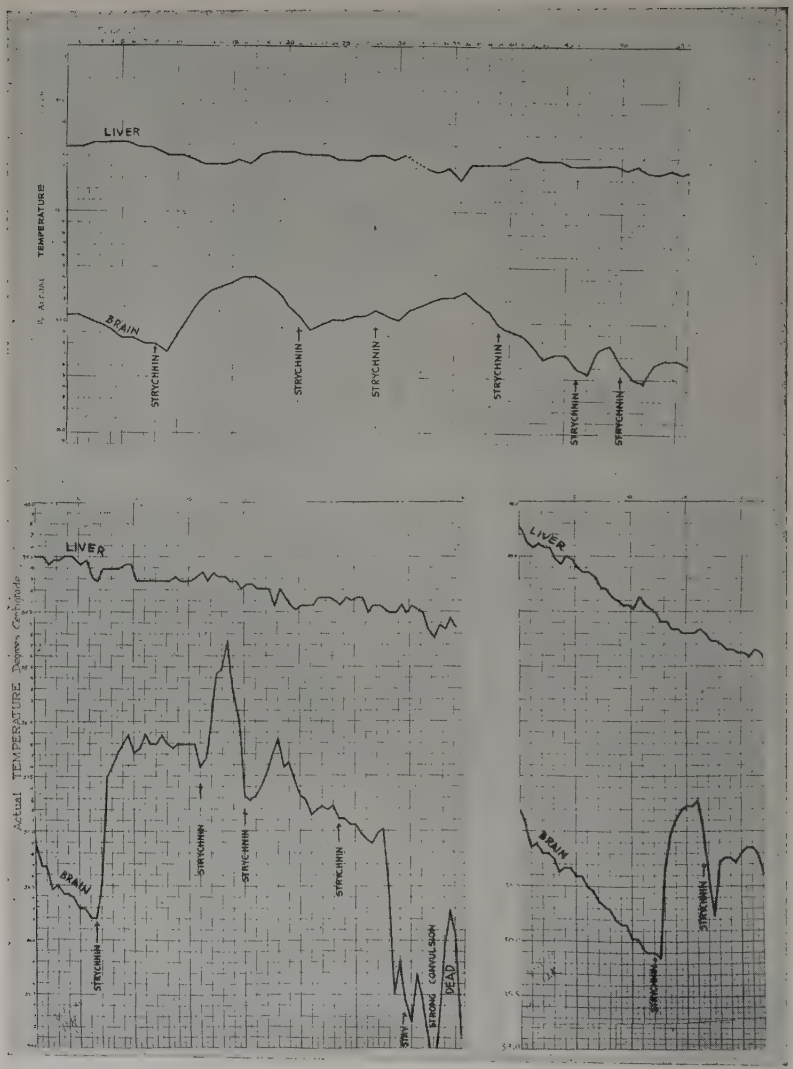

FIG. 42.—Effect of strychnin poisoning on the temperature of the brain. In each instance the temperature changes in the brain corresponded with the observed clinical effects of the injection.

muscles are not used, they are not so well organized and become weak. It is probable that play and exercise set in motion electric forces by means of which children are systematically built up into all-round physical efficiency.

Next in value to voluntary exercise, which exercises the driving nerve cell as well as the driven muscle, is electric stimulation of the muscle. Electric stimulation restores the muscle quite as well as voluntary stimulation, but electric stimulation does not as readily reorganize and build up the deteriorated nerve cells.

These points have been abundantly proved by clinical experience, especially by the results of the treatment of the multitude of cripples produced by the world war.

Inhalation Anesthesia

Ether

When an animal or a man is given unlimited ether anesthesia, several striking phenomena are observed. First, there is a period of excitement; second, a period of quiet anesthesia; third, a period of profound anesthesia, ending in death.

Period of Excitement.—During the period of excitement, the subject tends to struggle, the face is flushed, there are sweating, moderate or violent muscular action, rapid respiration, dilated pupils, elevated blood-pressure, accelerated pulse, increased output of adrenalin, hyperchromatism of the brain cells; the consumption of oxygen may be increased up to 150 per cent; of carbon dioxid up to 325 per cent (Alexander and Cserna)[3]; the H-ion concentration of the blood is increased; the electric conductivity of the brain is increased; the temperature of the brain is increased.

Osterhout,[4] Overton,[5] Meyer,[6] Lillie[7] and other observers have shown that ether anesthesia in lighter doses increases the permeability of the semi-permeable membranes of cells to the passage of ions. The activity of cells is governed by the state of permeability of their membranes to ions. This increased permeability renders the brain extremely excitable in light

ether anesthesia, and therefore it drives the organism to perform more work, as has been shown by Alexander and Cserna,[8] by our observations of hyperchromatism, by Elliott's demonstration of diminished adrenal content,[9] and by our demonstration of increased adrenalin output. The clinician sees striking evidence of this increased activation of the brain in the behavior of his patient under light ether. In cases of hyperthyroidism, the increased activation of the first stage of ether anesthesia is especially marked.

The clinical phenomena and the experimental findings lead us to suppose that ether causes a greatly increased production of electric energy, which escapes readily through the lowered resistance of the cell boundaries and of the synapses, and in consequence we may presume that heavy charges of electricity are freed from the cells, and run over the open nerve paths leading to the various muscles and glands. The muscular and glandular responses are as free from purposeful action as in a convulsion, but if the victim is held or injured during this stage then the electric action current is led over the corresponding facilitated paths and is concentrated on the muscles required for action, and other muscles become idle. If no contact directs the current then the outflow of energy is as general as in an epileptic convulsion; there are contractions of all the muscles; increased secretion of the salivary and the mucous glands; and increased sweating.

As we have stated, if the patient is restrained or injured during the first stage of anesthesia, then the muscles that usually respond receive all the collective electric force of the brain, and show almost supernatural power. If the anesthetic is withdrawn at this stage, the permeability of the cells returns to the normal, the struggle ceases, the flush fades from the face, the sweating ceases and the secretion of saliva and mucus rapidly becomes normal, the muscles come under voluntary control and are quiet. The individual appears normal with the exception of a slight fatigue.

Stage of Even Anesthesia.—If the administration of the anesthetic is steadily continued through the stage of excitement, or if the amount is increased, the period of struggle soon passes into a stage of complete relaxation. The face remains flushed,

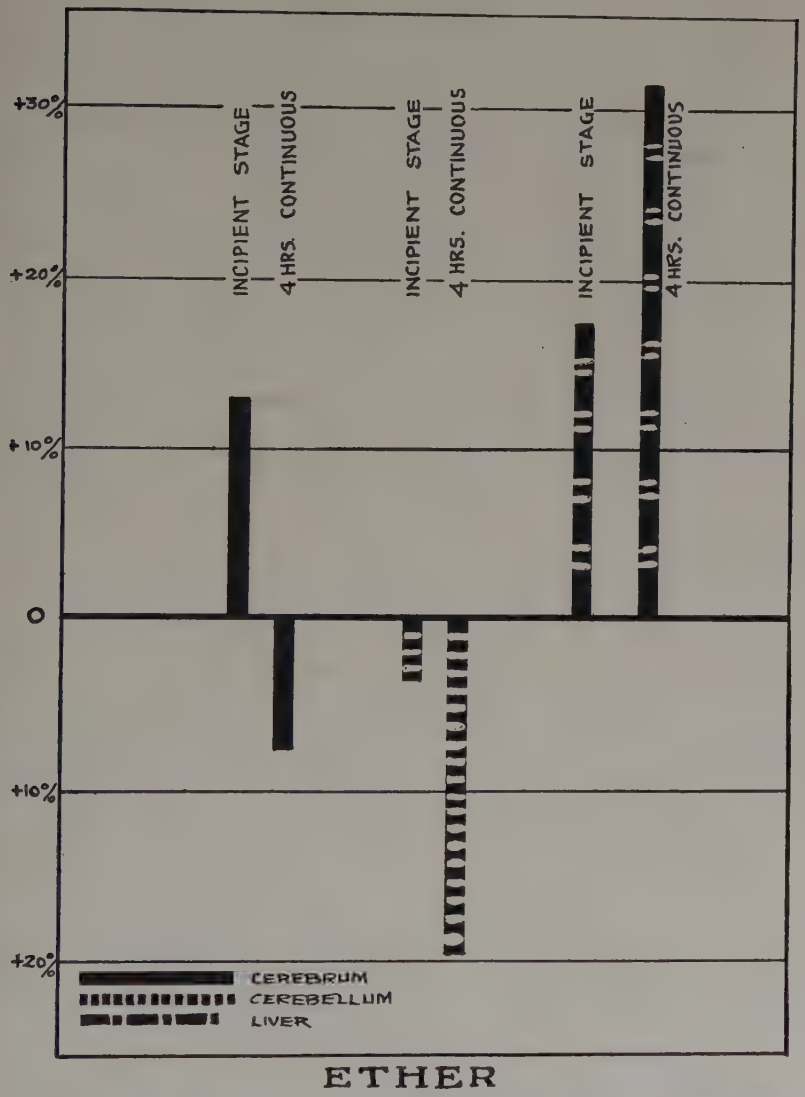

FIG. 43.—Early and late effects of ether anesthesia on the electric conductivity of the brain and of the liver.

although less so than in the stage of excitement; the eyes are less suffused; the skin is less moist; the saliva and mucus are less abundant. The H-ion concentration of the blood increases

with the increase of anesthesia. In this stage physical injury and restraint cause no marked muscular response.

This is in accord with the findings in our electric conductivity measurements, which showed a decreased conductivity of the cerebrum in deep ether anesthesia, as contrasted with the

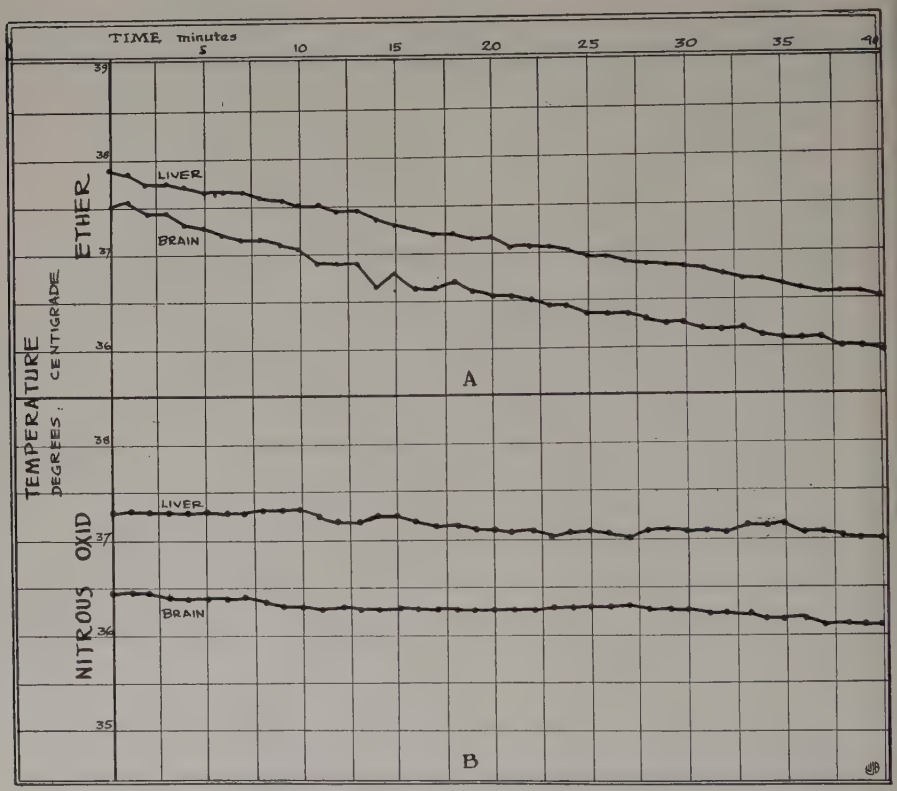

FIG. 44.—Comparative effects of prolonged ether and of prolonged nitrous oxid anesthesia on the temperature of the brain.

increased conductivity in the stage of excitement. (Fig. 43.) Measurements of the temperature of the brain show that following a brief rise in the initial stage the temperature falls progressively. (Fig. 44, A.) Moreover, as has been shown by Lillie,[10] McClendon [11] and others, during the stage of complete anesthesia the permeability of the cell and synaptic membranes

to the passage of ions is decreased in contrast to the increased permeability of the stage of excitement.

It seems probable that anesthesia is due to a block in the synaptic membranes like that which is supposed to occur in sleep, the difference being that in sleep the synaptic block is at once overcome by stimuli, hence is adaptive; whereas in anesthesia, the block is physical and non-adaptive. For this reason stimuli do not wholly awaken the patient, but nevertheless the afferent impulses reach the brain cells and stimulate them without purpose—exhausting the brain just as if no anesthetic had been given.

Profound Anesthesia: Death.—If the anesthesia is pushed still further, a point of saturation is reached at which the H-ion concentration of the blood passes the neutral point. This is the fatal point, for when the anesthetic causes actual acidity of the blood, death takes place immediately. Death, we assume, is due to the loss of difference in potential in the autonomic and sympathetic systems, as well as in the cerebrospinal system; hence, electric impulses cannot pass, and life ends.

The several parts of the brain differ greatly in their response to ether. It would be expected that the brain as a whole would be more markedly affected than other tissue, such, for example, as muscle, because the brain contains a greater proportion of lipoids, which are especially affected by ether. We would expect also that the order in which the different portions of the brain are affected would depend upon their relative irritability —the more irritable portions being affected first. This we find is true, for first consciousness is lost, then muscular activity, while the centers governing respiration and circulation are but slightly altered. Were the muscle cells more sensitive to anesthetics than the brain cells, then the function of the voluntary and of the involuntary muscular systems would fail before the function of the brain, and man would be paralyzed while conscious, as in curare poisoning; and since the respiratory and the circulatory muscles would fail, unconsciousness and death would follow the muscular paralysis, and no such state as anesthesia could be established. It is because of this difference between the muscle cells and the brain cells that anesthesia and not death is first produced by inhalation anesthesia.

When ether anesthesia is continued for four or more hours, these outstanding facts are noted:

1. Gradually less anesthetic is required.
2. An increasing period for recovery is required.
3. The brain cells, the liver cells and the adrenal cells show the same cytologic changes as are seen in exhaustion from other causes.
4. The reserve alkalinity is decreased.
5. The H-ion concentration of the blood is increased.
6. The electric conductivity of the brain is decreased; the electric conductivity of the liver is increased.
7. The temperature of the brain is decreased.
8. The individual is in a state of exhaustion, requiring a period of time for recovery about equal to that required for recovery from an equal degree of exhaustion from other causes.

Nitrous Oxid-Oxygen

In nitrous oxid-oxygen anesthesia, there is apparently an interference with the power of the brain cells to respond to stimulation by increased oxidation. This is demonstrated by the diminished response of the brain to the injection of adrenalin as shown by the slight increase in temperature as compared with the increase in temperature in normal animals and in animals under ether anesthesia. Therefore, the brain cells are able to respond to trauma and other stimuli only in inverse proportion to the depth of the anesthesia. The brain cells, therefore, are protected against shock. This is demonstrated by the hyperchromatic or normal appearance of the brain cells after prolonged nitrous oxid anesthesia; and by their normal appearance after shock-producing trauma under nitrous oxid-oxygen anesthesia as compared with their disintegration after like trauma under ether anesthesia. It is demonstrated also by the fact that the temperature of the brain is progressively decreased by long ether anesthesia, while it remains practically unchanged by nitrous oxid-oxygen anesthesia. (Fig. 49, B.)

These findings are in accord with the bipolar theory and with the conception that the brain is the primary seat of injury from

excessive stimulation. The effect of nitrous oxid is somewhat comparable to that of sleep, as our experiments have shown.

Because of the action of nitrous oxid on the intracellular oxidation, its use is fraught with danger unless it is skillfully administered. An animal may be much more quickly killed with nitrous oxid than with ether.

Hyperthyroidism

The essential content of the specific product of the thyroid gland is iodin. Iodin increases the electric conductivity of living tissue; iodin increases permeability; iodin increases the oxidative capacity of the brain.

It is known that stimulation of the nerve supply of the thyroid causes a discharge of its iodized product; hence, we may suppose that the output of iodin is in part at least under the control of the nervous system. In hyperthyroidism there is marked nervous activity. Cannon states that adrenalin activates the thyroid gland.[12] We assume that the stimulated gland throws out large amounts of activating iodin, which by so much facilitates permeability, increases the oxidative capacity of the central nervous system, hence increases the activation of the entire organism including the activation of the thyroid itself and of the adrenals. Oxidation is the basic process in metabolism; adrenalin increases oxidation; iodin increases electric conductance, hence increases metabolism.

Therefore, through the mediation of the nervous system, a reciprocal interaction is established among the thyroid, the adrenals, and the nervous system. Iodin alone, adrenalin alone, thyroid extract alone, emotion, exertion, or infection alone, each causes a "kinetic drive" with phenomena similar to those of hyperthyroidism.

If the foregoing interpretation be correct, then the drive of hyperthyroidism should be diminished by lessening the activity of any one of the three interacting organs—of the brain, by rest cure; of the thyroid, by its resection; of the adrenals, by the removal of a portion of their tissue, though up to the present time evidence of the positive value of the last-named procedure is still incomplete.

Nothing in surgery is more striking than the immediate benefit of the surgical treatment of hyperthyroidism. In the expression of the disease, in the behavior before, during and after operation, the patient with hyperthyroidism presents notable evidence in support of the bipolar theory.

The Infections—Fever

The effect on the organism of the injection of foreign proteins, as shown by Vaughan,[13] is similar to, if not identical with, the effect of infections. The mechanism of the action of the infections may therefore be regarded as the same as the mechanism of foreign protein reactions.

The injection of excessive amounts of foreign protein and the absorption of the toxins of infection produce similar effects, and involve certain essential parts of the same mechanism as the emotions and muscular exertion. This statement is based on the following phenomena: Each produces an increased output of adrenalin, a first stage of hyperchromatism of the brain-cells, followed later by chromatolysis, increased thyroid activity, increased body temperature. As a result of each, if excess fatigue is produced, the mechanism may be acutely worn down and completely overcome in death. The organism may be partly reduced by any one of these causes, carried further by another, and finally broken by still another. Their effects are interchangeable. Each produces increased electric conductivity of the brain in the acute phase, and in the stage of exhaustion a decreased electric conductivity of the brain. Each produces increased nervousness, and lowering of thresholds to other stimuli.

The first practical question is this: Is the response of the organism to an infection an imposed injurious mode of attack by the invading microörganism as a means of killing man and other animals, or is this response one of the evolved means by which man and animals defend themselves against the attacking microörganisms? Assuming it to be the latter, let us analyze the mechanism of this counter defense of man against the microörganism in the light of the bipolar theory. If our theory is correct we must point out the sequence of events

from the absorption of the toxin through the period of furious response to recovery or death, and point out the mechanisms which are involved. We must show that electric energy fabricated in the brain is an essential factor in the reaction. We must show that the muscles participate actively; that the adrenals are active; that the thyroid participates. We must show why a rise of temperature is of benefit; why there is no sweating in the first stage; why there may be chills. We must show why the temperature falls during the night. We must show why there is nervousness, loss of mental power, loss of muscular power. And last, and certainly not of least importance, we must show why, in an acute, overwhelming infection, there is shock and collapse, with diminished instead of increased metabolism as in the earlier stages; and why, under such circumstances, death is usually inevitable.

The Participation of the Brain.—It is common knowledge that deep narcotization with morphin reduces the power of the brain to drive the organism to transform potential energy into heat or into mental or muscular work or to express emotion. We may suppose that for the same reason morphin prevents the electric fish from transforming energy into electricity. In infections, morphin diminishes fever. In the acute phase following the injection of toxins, there is an increase in the conductivity of the brain; in the later stages there is a depression—morphin minimizes these changes.

The injection of foreign proteins, or of bacterial toxins, causes first hyperchromatism of the brain cells and later chromatolysis; but deep narcotization with morphin diminishes or prevents both the anaphylactic and the foreign protein systemic response and to the same degree prevents the changes in the brain cells.

Anaphylaxis and foreign proteins and bacterial toxins cause an increased output of adrenalin.[14] Deep narcotization by morphin prevents both. The significance of this point is that the nerves drive the adrenal glands to increase their output. This is proved by the fact that when the nerve supply to the adrenal glands is first severed, and no morphin is given, the output of adrenalin is not increased by the injection of foreign proteins, toxins, etc.

In patients in whom the brain cells are disintegrating as in enfeebled aged individuals, but slight fever is produced by even fatal infection. The highest fever and the most vigorous systemic response occur in the earlier periods of life when the brain is most active.

After decapitation, or when the muscles are cut off from connection with the brain, there is no febrile response to the injection of toxins. It would seem, therefore, that the brain cells respond to the presence of foreign proteins or of toxins by increased oxidation, thus causing an increased fabrication of electric energy which in turn drives the organism to make a febrile defense.

The Participation of the Muscles.—That the muscles are the principal mechanisms activated by the brain in the response to infection is suggested by the facts that (1) they produce from 50 to 75 per cent of the heat of the body; (2) they show fatigue and histologic change as a result of high fever; (3) they are the active agencies in chills.

The Participation of the Adrenals.—As has been shown by Elliott,[15] the output of adrenalin is increased by foreign proteins, toxins, etc.

The injection of adrenalin causes virtually all the phenomena of infection or of the injection of a foreign protein. In fevers, therefore, we may suppose that the dilated pupils, the flushed skin, the dilated nostrils, the opened air passages, the pounding heart, the elevated blood-pressure, as well as the fever itself, result in part from the action of adrenalin. Adrenalin alone causes leucocytosis, a phenomenon which is usually present in fever. In Addison's disease in which there is an adrenal insufficiency, the body temperature is subnormal. In this disease the defense of the organism against infection is diminished as is evidenced in part by the lessened rise in temperature.

The Participation of the Thyroid.—In myxedema, the body temperature is subnormal; and, though myxedematous subjects succumb to infections, they show little febrile reaction. In hyperthyroidism, infections cause abnormally high temperatures. Iodin alone causes most of the systemic symptoms of an infection. It is almost impossible to differentiate between an acute infection and iodoform poisoning. After operations

for hyperthyroidism one cannot distinguish with accuracy between the febrile reaction facilitated by the activation of the organism by the hyperactive thyroid and the activation due to an acute infection.

In hyperthyroidism there is a state of abnormal iodin facilitation, i.e., as we suppose, electric facilitation, and even an acute cold may cause a violent febrile response which may prove fatal.

In chronic infections, and even in prolonged acute infections such as tuberculosis, the thyroid is frequently hyperplastic.

In hyperthyroidism the thyroid is hypersensitive, hence hyperresponsive. Its enlargement is frequently demonstrable during an acute infection. Tonsillitis may cause the thyroid to enlarge and to remain enlarged; after the removal of infected tonsils, the thyroid sometimes returns promptly to its normal size.

In acute infections, often in chronic infections, therefore, the individual is obviously under the influence of increased thyroid activity. One of the evidences of this is the nervous state of the patient, which is but an indication that the nerve pathways have been facilitated by iodin for the more ready passage of the electric driving force.

In cases of hyperthyroidism, the nervousness is similar to that which is characteristic of all infections. The restlessness, the tossing and the sleeplessness may be regarded as phenomena of the facilitation of the electric conductivity by iodin and adrenalin.

On the day after a lobectomy has been performed, in an exquisitely nervous, excitable patient, the one conspicuous change —conspicuous to the nurse, and of infinite comfort to the patient—is the diminution of the intolerable restlessness, the intolerable excitability. We may suggest, therefore, that the nervousness in fever is due to the increased action of the thyroid.

Fever.—We have suggested the mechanism by means of which increased chemical activity, including fever, is produced, but the following question remains: What adaptive purpose is served by the increased temperature? This question is of peculiar significance in view of the obvious fact that this mode

of defense is itself injurious to the organism, sometimes causing permanent injury or death.

First of all, we may assume that the chemical invasion of bacteria can be met only by a chemical defense; that is, that the foreign protein molecule in a foreign environment will be split up more readily than is the living protein molecule of the defending organ; therefore, the more intense the chemical action of the defense, the more certainly and readily will the foreign protein, living or dead, be split up; that is to say, the defense of the body against foreign proteins, such as toxins, is a "purification by fire."

With each degree of rise in temperature in a physical or a biologic system, chemical activity—hence metabolism—is increased 10 per cent, and with each degree of rise in temperature, the electric conductivity is increased 2.5 per cent.

The organism must maintain a standard of chemical purity, and this standard, as we suppose, is reached by burning the foreign proteins in the furnace of the living through intense chemical action, intense oxidation. The foregoing does not apply to the defense of the phagocytes, nor to defense by antibodies, but only to the defense against foreign proteins.

Dry Skin.—If the full benefit of the increased body temperature is to be secured, heat must be retained in the body. Sweating produces cooling of the body as the result of evaporation. Hence, in infections we have the high temperature with a dry skin in contrast to the active sweating which results from muscular exertion, when heat is not desired.

Chills.—It is obvious that the active muscular contractions of the entire body in the chills which frequently accompany the inauguration of the response to an infection are but an added means of increasing chemical metabolism, just as shivering is a part of the process of increasing metabolism on a cold day. On the other hand, it is equally obvious that a man in surgical shock cannot shiver, because the electrical mechanism that fabricates the chill has broken down.

Why does the temperature fall during the night?—The foregoing discussion suggests that it is because the brain, being the driving battery, must be recharged. This recharging process is probably accomplished during sleep, but in order that the

chemical defense may be as little interrupted as possible the periods of sleep are light and short. During sleep the temperature falls because the brain is driving the mechanism less forcibly. All of the brain does not sleep, however, nor do all the glands or involuntary muscles, hence the temperature remains above normal, although it usually falls below the day-level.

Thirst.—When the biologic bipolar mechanism is excessively driven in a strong defense against foreign living and dead proteins, large quantities of water are used. The need of abundant water in the operation of a bipolar mechanism has been described; that that need is magnified in the mechanism driven by infection, is obvious. This need is manifested by thirst.

The Mechanism of Collapse and Death in Overwhelming Infections.—Gazing directly at the sun breaks down the photo-electro-chemical mechanism of sight. When the sensitive areas and nerves of the body are heavily traumatized or when the individual has been subjected to an overwhelming emotion, the internal lesions of the brain cells are so great that they cannot continue their normal function and become unable to transform potential energy into electric energy at a normal rate, so that the power to perform muscular work, mental work, and glandular work is lessened; the power to maintain the blood-pressure is diminished; the power to produce the normal amount of body heat is lost, and the state called *shock* is produced. Since foreign proteins drive the brain cells just as they are driven by emotion or by physical injury it follows that an excessive foreign protein stimulation, such as results from perforation of the intestines, from the penetration of an abscess into a large absorbing cavity, from anaphylaxis, may drive the brain cells to their ultimate destruction—to death.

It is not surprising, then, that precisely the same principles of treatment apply to the shock of acute infection as to traumatic shock; that the same agents that aggravate shock, aggravate fevers, i.e., injury, fear, worry, loss of sleep, ether and chloroform anesthesia, muscular exertion, etc.; and on the other hand, that precisely the same principles of treatment are ap-

plicable to both the acute and the chronic forms of infection, viz., rest, fluids, morphin, sleep.

Infection, like any other cause of exhaustion, may be regarded as an activation of the same bipolar mechanism; each causes an increased fabrication of electric energy; in each case the fabrication of the electric energy is activated by the same organs; in each case, when the drive has been so intense or so prolonged as to produce a permanent change in the driving battery or in any of the activators, *exhaustion* follows. Anaphylaxis, with its momentous chemical blow, may be likened to a bolt of lightning striking an electric battery.

The suggested interpretation of this group of clinical phenomena which we have selected for discussion is sufficient to indicate the basis for our belief that all of the phenomena of life, normal and pathological, can be described in electrochemical terms—are the manifestations of the variations in the operation of one or another essential constituent part of a bipolar mechanism.

It follows, logically, that the restoration of the organism, whatever the primary cause of its derangement, requires, in addition to the removal or adjustment of the primarily affected part, the same essential electro-chemical measures, the restoration of the primary batteries by water, the promotion of oxidation, rest and sleep.

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CHAPTER VIII

A Suggested Bipolar Interpretation of Cancer

The three outstanding facts about cancer are (1) that it originates only in the living; (2) that the cancer cells thrive at the expense of the cells of the tissues in which they develop; and (3) that the cancer cells have a much higher capacity for multiplication and growth than do normal living cells.

The fundamental requirement in presenting any theory which may explain the nature of cancer, therefore, demands primarily that we discover whether normal cells and cancer cells are distinguished by any physical characteristics which may explain the superior ability of the cancer cell to multiply at the expense of other tissues in which it grows.

The best known example of growth energy is that initiated by fertilization in reproduction. The outstanding facts regarding fertilization which may throw light on the cancer problem are:

1. The spermatozoön has the properties of the nucleus of the ovum with which it unites. (Fig. 45.)
2. The spermatozoön may be said to reinforce the nucleus and as a consequence,
3. The quiescent negative ovum flares up in active metabolism and growth and in consequence shows a striking change in its internal structure (Fig. 46); and it assumes electrical properties, i.e., electricity is a constant phenomenon from the moment of fertilization, so long as the life of the new individual lasts.

This comparison of the processes of the multiplication of cancer cells with that of fertilized cells is no new conception, the similarity of the nuclear changes having even led to the supposition by some that malignant processes actually were the

result of some form of fertilization. Moreover, the cyclic variations in the growth of tumors correspond to the cyclic changes in nuclear and mitotic activities which have been observed in protozoas.

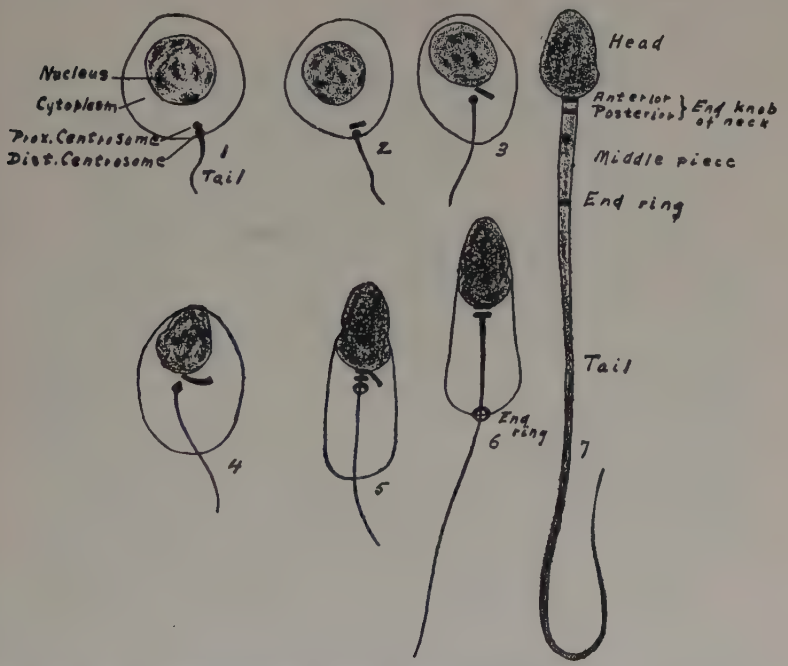

FIG. 45.—The metamorphosis of the nucleus of the spermatid into the head of the spermatozoön. Note the concentration of the nuclear material in the head of the spermatozoön. (From Jordan and Ferguson. Textbook of Histology. New York, 1916, p. 484.)

The whole histologic picture of malignancy indicates that it is primarily nuclear in origin as is suggested especially by the large nuclear plasma ratio which is maintained either by the size of a single nucleus or by multiple nuclei (Figs. 47 and 48), by nuclear hyperchromatism in the active stages and by the shrinkage of the nuclei in the degenerating or necrosed areas.

Physical chemists (McClendon, Lillie, Loeb, etc.) have shown that fertilization of the ovum is attended by an increase in permeability; that the state of activity of cells, whether in the course of normal functioning or in multiplying, is attended

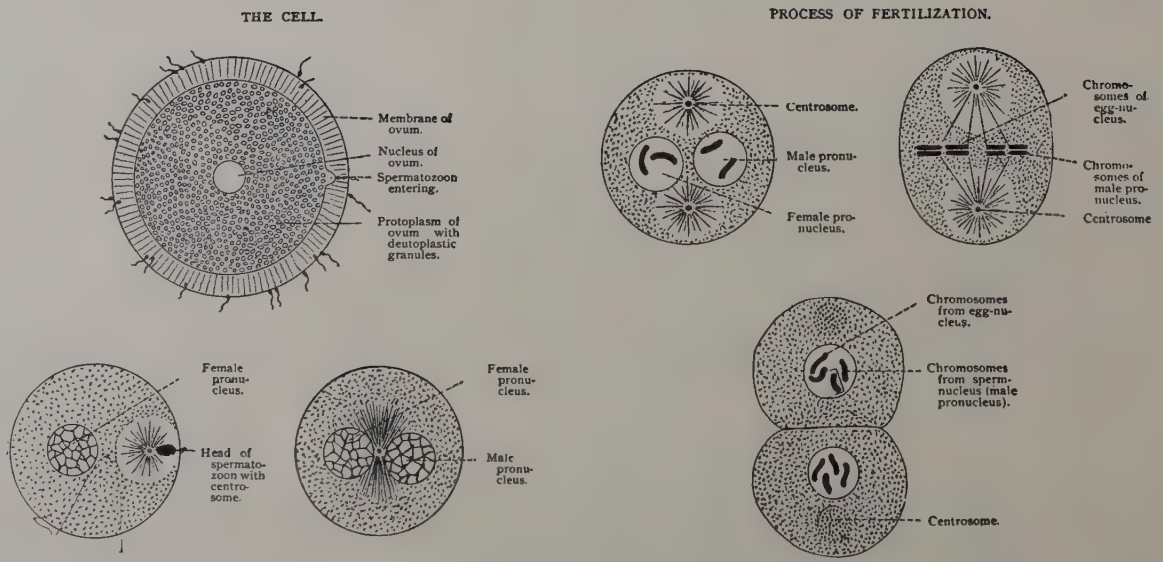

FIG. 46.—Schematic representation of the intracellular changes following fertilization. (From Böhm, Davidoff, Huber. Textbook of Histology. Philadelphia, 1909, pp. 72 and 73.)

by an increase in permeability. On the basis, therefore, that the processes of cell division in cancer are analogous to the processes of cell division in fertilized cells we have applied certain biophysical methods of measurement to various types of tumors, both benign and malignant, and our results appear to

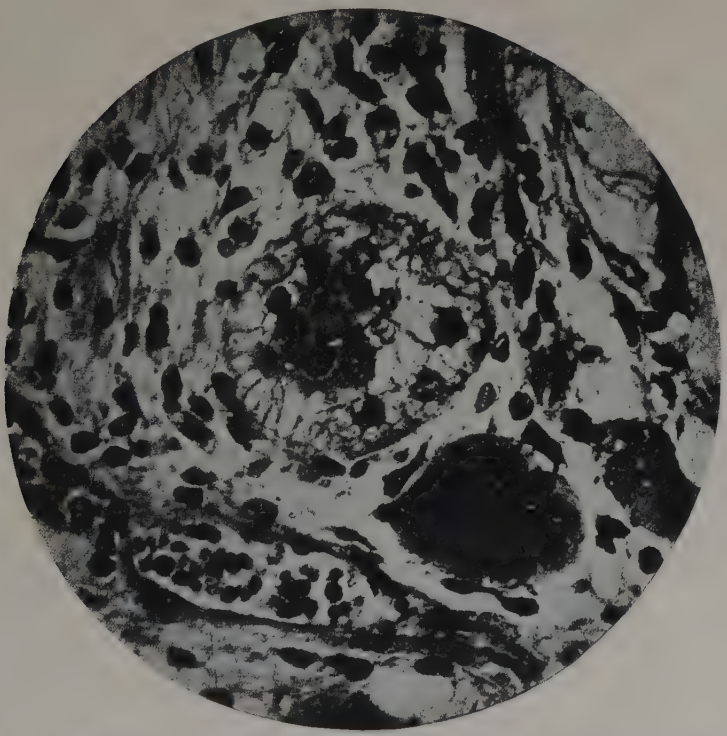

FIG. 47.—Spider cell with multiple nuclei from rhabdomyosarcoma. (From Ewing: Neoplastic Diseases. Philadelphia, 1922, p. 218.)

indicate that the nature of cancer falls within the domain of the bipolar theory.

Certain analogies between cancer and the pyogenic infections may aid in this interpretation. Cancer cells multiply, bacteria multiply, each finds restraint in certain tissues. Neither cancer nor pyogenic infection commonly attacks tissues of high oxidative capacity; thus neither cancer nor pyogenic infection primarily attacks the heart muscle, the voluntary muscles, the

cortex of the brain, the normal thyroid gland, the liver, the parenchyma of the kidney, the spleen, etc. No enzyme, no specific chemical property has been found to account for this fact. These are tissues of high chemical activities; these organs are homologous in structure and their cells are closely approxi-

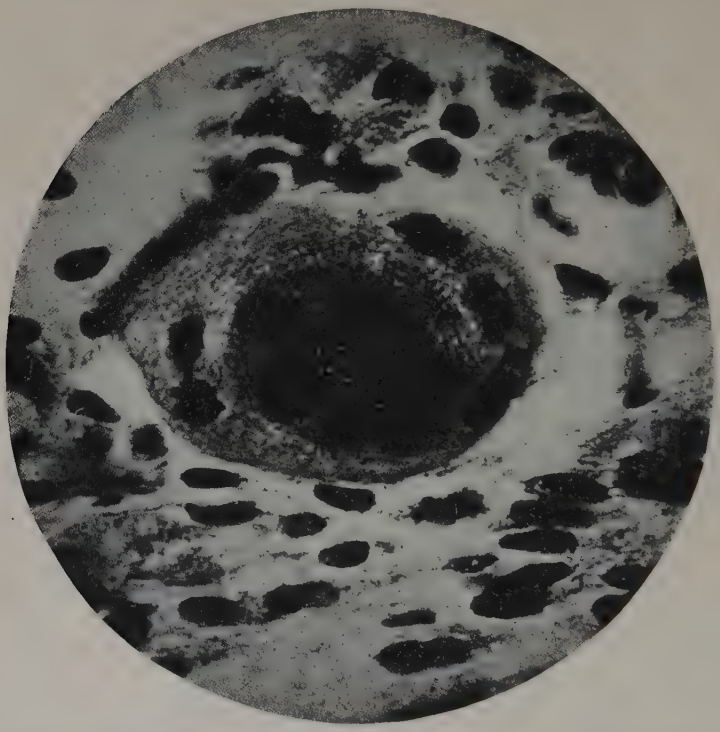

FIG. 48.—Striated giant cell in rhabdomyosarcoma. (From Ewing: Neoplastic Diseases. Philadelphia, 1922, p. 219.)

mated and bathed in fluid; in other words, these organs are concentrated cell suspensions. Neither infection nor cancer attacks primarily the anatomically and physiologically intact surface layers of cells like the skin and mucous membranes, the latter in turn being an electrically charged cell suspension system. They attack these after the normal cells are disturbed.

Our first generalization then is that cancer originates not in the *midst* of a cell suspension such as the cellular organs but

at the boundary points between highly cellular and less cellular structures. These less cellular structures—subcutaneous, submucous—are successfully attacked by cancer or infection only when the cellular defense is broken down; in the case of a pyogenic invasion a single break in the line of defense may be sufficient for entrance; cancer depends rather upon the gradual lessening of the defense which results from the frequent breaking down and building up. Once the rapid infection or the slower cancer has passed this first line of defense, each follows the path of least resistance—namely, the lymphatic channels and the connective tissue, rather than attacking the solid cellular organs.

Another analogy between cancer and infection is found in the fact that each obeys laws of cell division and growth which apparently are the same as those which govern the cells of the host.

Both cancer and infection are repulsed by vigorous metabolic activity within the defending structures; thus, as we have already noted, the heart muscle, the voluntary muscles, the normal thyroid, are relatively immune. To this fact, we may add the significant fact that bacteria do not attack the most active part of the cell itself; that is, the nucleus of the cell is highly immune to pyogenic invasion. To this statement it should be added that the cell nucleus and bacteria show a similar reaction to stains. Finally, unlike the normal cells of animals, cancer cells and bacteria have no specific function; they possess growth energy only.

From this argument we conclude that the area of oxidating surface in the nucleus of a cell as compared with the area of oxidating surface in the cytoplasm is but another way of expressing the nuclear plasma relationship and signifies that the larger the nucleus in comparison with the cytoplasm the greater the energy potential of the cell. Thus, if two cells have an identical organization, an identical energy potential, then, with respect to each other in the competition for nutrition their chances are even, but if in one of two adjacent cells the size and organization of the nucleus are such as to give it a greater capacity for oxidation, hence a greater demand for nutrition,

then the cell of comparatively low oxidative capacity will suffer in the competition and will break down in starvation.

As we have stated above, in cancer cells the nuclear plasma relation quantitatively resembles that of fertilized cells. Before fertilization the ovum in itself is so lacking in organization and hence in oxidative capacity that there is apparently little or no difference in potential between its nucleus and its cytoplasm—it carries little or no electric charge, it is inactive, negative. But when the nucleus of the ovum is reinforced by the nucleus-like spermatozoön there is at once established a difference in energy potential within the cell, oxidation becomes rapid, nutrition is demanded, the size of the nucleus increases, mitosis is inaugurated, cell division occurs.

As we have stated, our interpretation of cancer assumes that the difference between the cancer cell and the neighboring cells of lower potential is analogous to the difference between the unfertilized and the fertilized ovum. The analogy ends, however, once the mechanism of cell division has been established, for cancer cells have little or no differentiation.

If the foregoing biophysical interpretation is correct, then cancer tissue must meet the following biophysical requirements: (1) the cancer cells must have a high capacity for the storage of electric charges; and (2) the conductivity of cancer tissue must show specific variations from the conductivity of normal tissues. That is, if our assumption is correct, then the lipoid films of the cancer cells, of the normal cells and of the fertilized cells would take electric charges in a direct ratio to the combined surface area of their lipoid films. For instance, though in its external appearance a fertilized fish egg is apparently the same as an unfertilized egg, one would expect the former to show a higher capacity than the latter; one would expect that the capacity of cancer cells would be higher than that of normal cells; one would expect that radiation would lower the capacity of cells; one would expect to find a higher capacity in such cellular tissues as the brain, liver, muscles, adrenals, thyroid, spleen, pancreas, than in such indifferent tissues as connective tissue and fat.

Our first biophysical investigation of cancer consisted in a series of comparative measurements of the electric conductivity

of normal and of pathological tissues (Appendix C). The clinical tissues measured included malignant and benign tumors

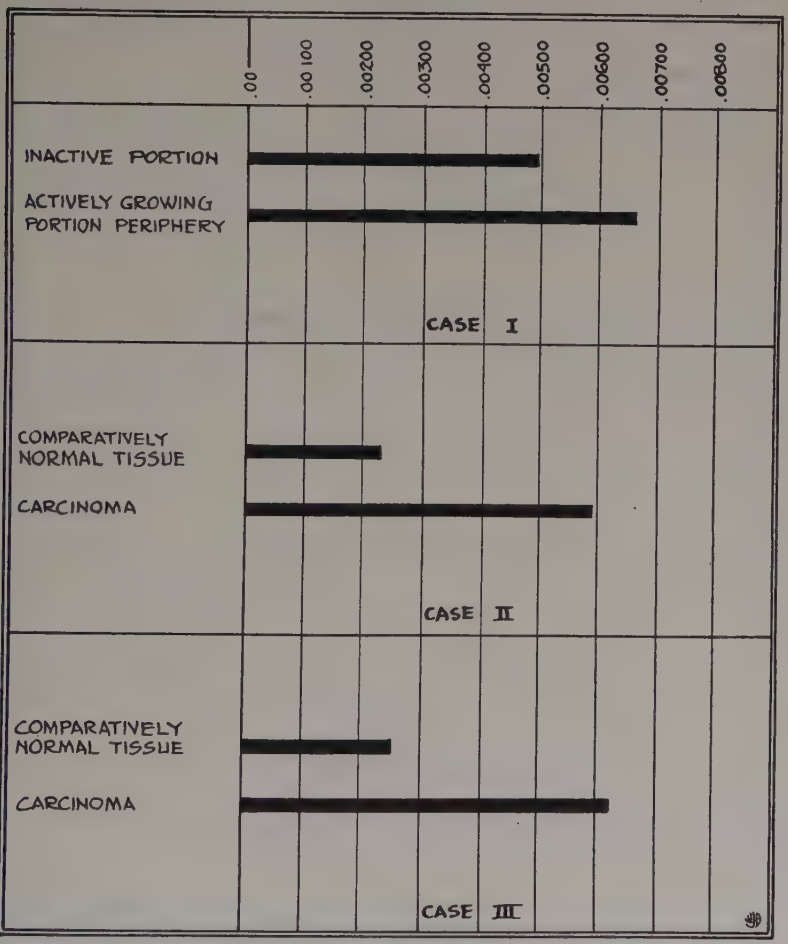

FIG. 49.—Comparison of the electric conductivity of carcinoma of the breast with that of comparatively normal portions of the same gland (3 cases).

of the breast and of the uterus, ulcer and carcinoma of the stomach, carcinoma of the rectum, malignant and benign tumors of the mouth, jaws, and neck, X-ray burns and various types of goiters—hyperplasia, fetal adenoma, multiple adenoma, toxic

adenoma, exophthalmic goiter, simple colloid goiter. The following were the significant findings:

1. In all instances in which comparative measurements were made the conductivity of the malignant growth was higher than that of a normal portion of the same organ. (Figs. 49 and 50.)

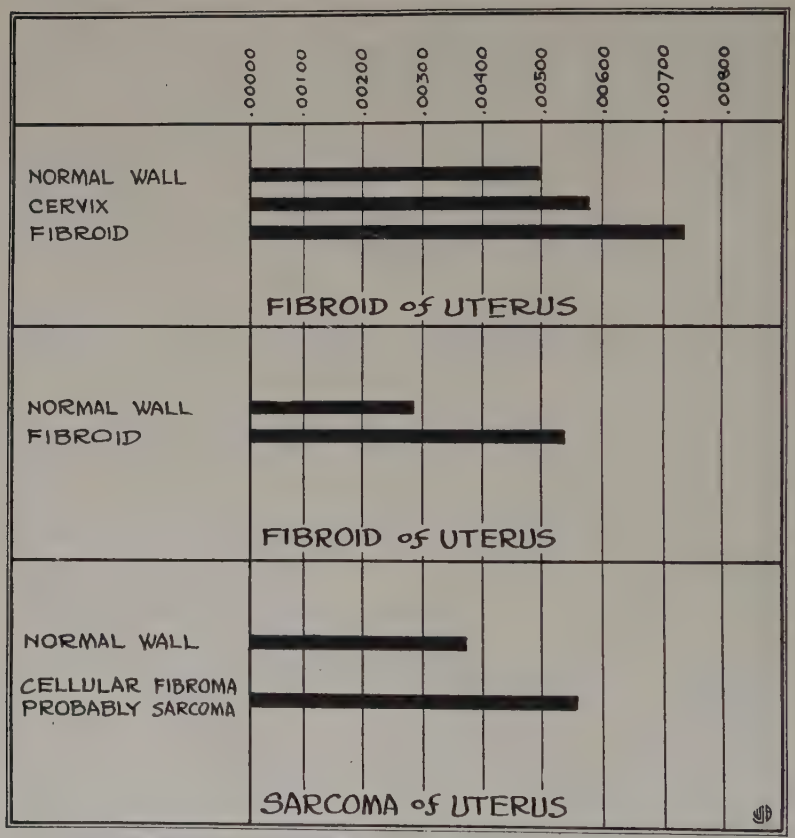

FIG. 50.—Comparison of the electric conductivity of neoplasms of the uterus with that of comparatively normal tissues of the same organ (3 cases).

2. The outer growing parts of cancers showed a high conductivity in contrast with the conductivity of the central non-growing parts.

3. Among the goiters studied the highest conductivities

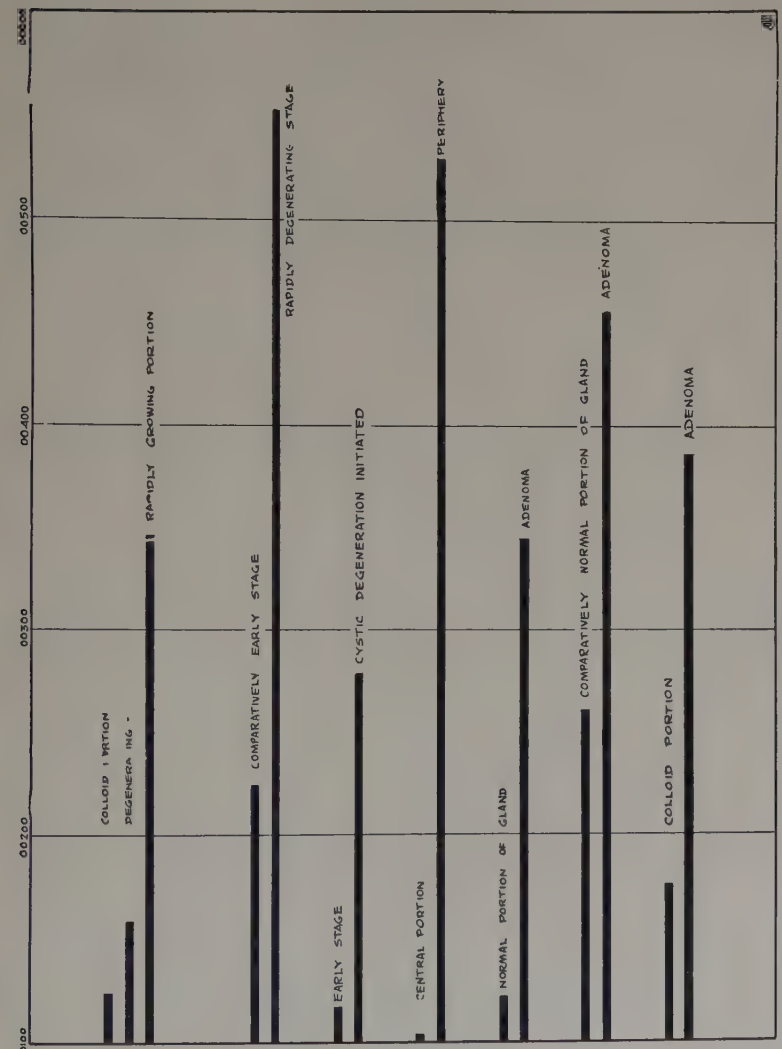

FIG. 51.—Comparison of the electric conductivity of different types of goiter with that of the comparatively normal or inactive portions of the same gland (7 cases).

were found in the degenerating adenomata and the malignant thyroids; the conductivities of the hyperplastic thyroids were lower; and the conductivities of the colloid goiters were the lowest of any of the pathological tissues studied. (Fig. 51.)

These measurements were made with an alternating current of 1000 cycles. This comparatively low frequency of current would probably find the path of lowest resistance, in large part, undoubtedly, through the intercellular tissues.

Extending this line of inquiry, the theoretical requirement that cancer tissue must have a high capacity for the storage of electric charges, was given to Dr. Fricke and Dr. Morse, of the Biophysical Department of the Cleveland Clinic Foundation for investigation. Dr. Fricke has derived a formula and devised an apparatus whereby frequencies ranging from 800 to 4½ million or more cycles can be applied to the cells under investigation. The physical estimations of the capacity of normal tissue and of benign and malignant tumors thus far made are as follows:

Eighty specimens from 58 cases have been investigated, including 15 carcinomata of various types, 3 sarcomata, 3 benign tumors and 16 goiters of various types. In the arbitrary units employed normal tissues have ranged from 28.2 m. m. f. for fatty tissue, and 60 to 180 m. m. f. for connective tissue to 600 m. m. f. for the normal uterus. All of the carcinomata have had a relatively high capacity ranging from 660 to 1920 m. m. f. in the actively growing portions of the growth. The degenerated portions of the growth have had a lower capacity and radiated tissues have been much lower, the tissue in one radiated case showing as low a capacity as 180 m. m. f. Thus far in every case studied the tissue in which the cancer had developed had a lower capacity than the cancer itself. This difference has been particularly marked in the case of carcinomata of the breast in which the capacity of the adjacent glandular connective or fatty tissue has often been less than 1/10 that of the malignant tissue. Among the goiters colloid goiters have shown the highest capacity of any tissues studied, as much as 4560 m. m. f. in one case, the average being in the neighborhood of 2400. This finding is of prime significance in view of the fact that cancer of the thyroid never develops in a colloid goiter.

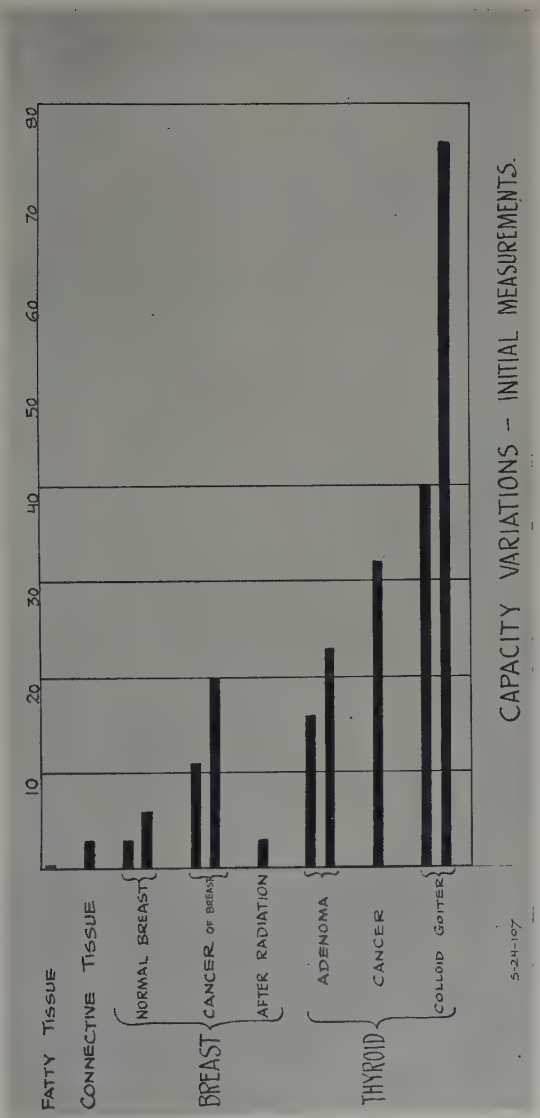

FIG. 52.—Comparison of the electric capacity of normal and of neoplastic tissues.

Adenomas and hyperplastic thyroids have, as a rule, had a low capacity for glandular tissue which in general seemed to show a somewhat higher capacity than other tissue. Connective tissue has usually a very low value, between one and three, and the capacity of fatty tissue may be as low as 28.2 m. m. f., while an active inflammatory process may show a capacity of 1200 m. m. f. (Fig. 52.) These measurements run parallel relatively to the conductivity measurements previously made by Miss Hosmer and Miss Rowland.

The findings in these researches suggested that much of the story of cancer may ultimately be derived from conductivity and capacity measurements. These findings moreover are in accord with the histological picture presented by the microscope. The microscope indicates the general structure which in turn indicates the capacity of the cell for work, multiplication, function, etc. A further striking parallel between the cytologic picture and biophysical findings is found in the fact that cells which have been subjected to lethal X-ray or radium radiation show loss of differential stainability and in our laboratory Fricke and Morse have shown that heavily radiated tissue almost wholly loses its capacity.

Armed with these physical facts, let us see to what extent some of the well-known facts regarding cancer may be harmonized. First of all, on the basis of electric potential, implying as it does oxidative capacity, if two cells are side by side competing for food, the one having the higher potential, such as the fertilized cell or the cancer cell, starves out, and if the higher potential—higher oxidative capacity—persists long enough, destroys the ordinary tissue. Among cells with equal capacity, such as those within the cancer itself or the daughter cells of the fertilized ovum, division occurs evenly, no one starves another. This fact explains why cancer does not arise either primarily or secondarily in that fiery furnace, the heart muscle, or in other muscles, or in the cortex of the brain, or in the normal thyroid gland, etc. It also indicates why when from some cause the capacity of an epithelial cell resting on subcutaneous or submucous cells of low capacity has been increased until it is equal to the capacity resulting from fertilization, that cell will easily rob the neighboring inactive tissues of their

nutrition and will supplant them, just as the vigorous growing weed overgrows and supplants the highly differentiated less vigorous domestic crops.

A consideration of the conditions under which cancer develops in the thyroid gland is illuminating. First, cancer almost never develops in the normal thyroid or in colloid goiters but over 90 per cent of cancers of the thyroid arise in the fetal adenomata. On the basis of our premise a physicist would have predicted that that would be the case, even though he knew nothing about the actual incidence of cancer in the thyroid gland; for, as has been stated above, the capacity measurements made by Fricke and Morse show that both colloid goiter and the normal gland have a higher capacity than cancer of the thyroid, while the capacity of fetal adenoma is lower than that of cancer.

Again let us consider one of the most common sites of cancer origin—the breast. Here is an organ whose structure contains epithelial cells, the capacity of which is low. It follows that when some circumstances bring into contact with these low capacity epithelial cells, cells with a relatively high potential, the latter multiply at the expense of the other breast tissue. The capacity of cancer of the breast is from two to ten times higher than the capacity of normal breast tissue. The capacity of the tissue near the cancer mass is somewhat higher than that of normal tissue. In general, benign tumors have a higher capacity than that of the organ in which they grow, e.g., the capacity of a fibroid is higher than that of the normal uterus.

There is a general analogy to this conception of the law governing incidence of cancer in the various tissues, in the tables of Voit, which show that in starvation the weight of the brain and of the heart muscle does not change, the reason being that these tissues, the metabolism of which is at a higher rate than that of other tissues, consume the nutrition at the expense of the others. For the same reason a fetus thrives up to the point of starvation of the mother.

This conception might explain the higher incidence of cancer in old age when the generally falling metabolism would diminish the already low defense of the tissues of low capacity and lead to an inequality in an already wavering balance between the

capacities of neighboring cells. Moreover, the older and the feebler the subject, the slower the growth of cancer and the better the prognosis; and *per contra* the younger and more vigorous the subject, the shorter the course, the more fatal the cancer. But youth has fewer cancers than old age. Our theory interprets this antithesis as follows: In the general activity of all tissues in youth it would be unusual to find the potential of any one cell raised above that of its equally vigorous neighbors, but once so phenomenal a cell has been produced, its growth energy would be enormous, rapid and fatal. In old age, on the other hand, with its universal decline in activity, although a cell may more readily become endowed with the equivalent of fertilization so that its potential and its capacity may become higher than those of its feeble neighbors, yet it would have a very moderate growth energy. In fact, cancer in the aged and feeble inevitably would appear just above the low level of low vitality, in youth just above the high level of youthful vitality. In youth the cancer must be virile; in age it must be feebler. Thus, in experimental studies cancers are not transplanted to the muscles, nor to the liver, nor to the heart, nor to the brain, but to the more negative tissues; it is the subcutaneous quiescent breast tissue that is generally selected as the site for the graft.

If one could plant a self-limited bacterium in the nucleus of a cell, its added oxidation might augment the nucleus in a manner analogous to the augmentation of the nucleus of the ovum by the spermatozoön so that in consequence cell division would be forced. Or if one could draw the nucleus out of one cell and insert it into a sister cell, thus reinforcing its nucleus, the energy potential of the latter cell would be increased, its nutrition intake increased and cell division would follow, i.e., a cancer would be produced.

The interpretation of another fact is made possible by the bipolar theory, namely, the like action of X-ray and radium on cancer and on fertilization. The effect of radiation is to interfere with the mechanism in the cell for the creation and storage of electric charges, an interference which as effectively prevents growth and function as does the permanent discharge of any battery.

An interpretation of still another group of facts is suggested by the bipolar theory, namely, that sarcomata appear early in life and are disseminated, while epithelial growths appear later in life. A possible though admittedly not a clear interpretation of this differentiation would be that cells distributed by the blood lodge in the more vigorous oxidizing organs such as the muscles, glands, etc., while the cells spread by the lymphatics reach the lymph glands, whose metabolism is relatively low. Therefore, the older and the feebler the patient the more probable it is that the cancer cells which are most likely to metastasize will be those that reach the lymphatic glands, whose flame is burning low. Again, when the potential of a cell in the high tension thyroid rises above that of its fellows and in consequence multiplies at their expense in a fetal adenoma one would expect a wide extension of these cells and such is the case.

Certain everyday facts about treatment are also open to a biophysical interpretation. Thus, if a cancer is entirely removed early, no return is seen; whereas if a cancer is stimulated by injury, by partial operation, by inflammation, by chemical agents, by X-ray, by radium, by heat, by electricity, the resultant struggle and survival kill off the weaker cells, leaving the stronger. When a massive treatment is given, any cells which survive will be the fittest, hence the return growth will be at the pace of the strongest, the fittest cancer cells, not of the less strong cells that did not survive. The combination of diminishing vigor on the one hand and a stepping up on the other, theoretically would bring about the unbalance required for cancer.

Pyogenic Infection.—We have already mentioned certain analogies between cancer and pyogenic infections. Certain further biologic principles governing infection which appear to be the same as those governing cancer may be cited. The resemblance between cancer and infection has been noted by many observers. Pyogenic bacteria may be regarded as free nuclei, like the fragmented nuclei seen in many unicellular organisms. If we regard the law of universal bipolarism as a necessary condition by means of which a difference in potential is created and oxidation controlled with resultant electric

charges and maintenance of potential, we interpret bacteria as free nuclei depending for their common negative pole on the common colloids such as mud, soil, sea-water, etc., and the colloids in the tissues and fluids of animals. Bacteria then would multiply as free nuclei.

According to our conception a cancer cell is a bipolar mechanism within which the nucleus is the positive, the cytoplasm the negative pole; bacteria are positive poles with lymph and tissue juices as a common negative pole. According to this conception the cancer cell and the bacterium are in a common class of high potential invaders. Now the bacterium, like the cancer cell, must depend on its ability to compete with the cells of the organism for nutrition. It is probably a consequence of this fact that bacteria, like cancer, cannot primarily compete with the cells of the organs which have a high metabolism. Bacteria, like cancer, attack best the negative tissues, the subcutaneous tissues, the fascia, the bone, surfaces that have been irritated. Bacteria stain like nuclei; bacteria almost never attack nuclei of cells, almost never muscles, most seldom of all the heart muscle. Bacteria tend to spread by the adynamic lymphatic system rather than by the dynamic blood-stream. However, as in cancer, if bacteria are potent enough, i.e., have the required potential to multiply in the blood stream those bacteria are more apt to kill and to kill early. Both bacteria and cancer provoke white cell invasion in their advancing line; both bacteria and cancer cells multiply at the expense of their host; both may form tumors; both cause reactions; both interfere with function; both are selective as to the attacked organs, as to invasion.

As to the problems suggested by this discussion it would seem that in polarization-capacity estimations we may have one more criterion for the diagnosis of cancer, for the microscope reveals the films which hold the charges. The microscopic picture represents the static, the capacity measurement, the dynamic state of the cell. Even if this should not become a method of operating room diagnosis, it may at least supplement the microscope. We may perhaps find in this new biophysical method not only a means of diagnosis but one of prognosis as well—low capacity relation of the growth to the adjacent tissues would

theoretically mean low malignancy and *vice versa*. There is one more and a unique possibility, namely, that after the effects of radiation on capacity have been studied further it may be that the capacity of a tumor may at last furnish the key to the amount of radiation required as a lethal dose; or indeed may determine whether any dose that the normal tissue of the organism could endure would cure, so that futile efforts could be avoided.

CHAPTER IX

A Suggested Bipolar Interpretation of the Mechanism of Memory

If our conception that living processes are due to the operation of electrical forces acting in a bipolar mechanism is correct, then mental processes such as ideation and memory cannot be exceptions to what we conceive to be an all-embracing law. The intangible nature of these processes and the fact that we are dealing with infinitesimal forces and infinitesimal particles of matter make a demonstrable explanation impossible. Nevertheless, on the basis of what is demonstrable, both by the gross and microscopic structure of the brain, by the demonstrated laws which govern electric forces and by certain experimental evidence, we conceive that mental processes are subject to the bipolar law.

The white matter of the brain and cord like the film around the cell, around the nucleus and around the spherules within the brain cells is a lipoid substance and hence, like the lipoid films of the cells, it is dielectric—it has electric capacity, as has been shown experimentally by George H. Crile. Like the film around the cells, the white matter contains also certain electrolytes, principal among which are potassium, calcium, phosphorus and sulphur.

It is well known that the passage of electricity through a substance tends to orientate the molecules of that substance along the direction of the electric current. One can easily conceive therefore that the first effect of an electrical impact upon the lipoid material of the white matter of the brain from the cells—batteries—in the gray matter would be to orientate the fatty molecules into a chain-like arrangement. As this orientation would progress, as progress it must under successive electrical impacts, these chains of fatty molecules would be extended.

Thus, for example, a ray of light impinging upon the retina would set free successively the electrical charges of the surface cells and of the amplifying cells of the retina, these charges being conveyed by the optic nerve to cells in the gray matter of the brain, which in turn would be discharged with the resultant establishment of a chain of ionized lipoid molecules within the white matter. By a second similar impact, that fatty chain would be extended and rendered more stable. This orientation of the molecules in the lipoid substance of the white matter we may imagine to be accomplished by a sort of replacement process.

According to our hypothesis, as this "excitation wave" progresses, ions of potassium are progressively displaced from molecule to molecule along the path of orientated lipoid molecules so that a progressive chain of potassium remains to constitute the essential conducting characteristics of the nerve paths.

This would be in accord, as suggested by Professor Millikan in a personal communication, with certain experiments going on in his laboratory in which sodium atoms are driven through the walls of a sodium glass electric light bulb. By forcing a high voltage current through the vacuum the electronic bombardment forced the sodium atom out of the first molecule with which it came in contact. This displaced sodium atom collided with and replaced the sodium atom in the next molecule and so on until the last sodium atom lying next to the vacuum in the electric light bulb was displaced to the free surface on the inside of the bulb.

We may imagine that if instead of the vacuum, the bulb were filled with lipins having a certain resistance, the electronic bombardment might well have carried these sodium atoms along the line of strain and so have made a track of orientated lipoid chains holding within them the sodium ions. Within the white matter of the brain then, we would conceive that the potassium or sodium or chlorin atoms could be pushed through the membrane of a cell of the gray matter upon the receipt of an electric impulse, and so on from cell to cell by the continuance of this replacement process, electrolytic chains associated with the molecules would be established, along the line of which the passage of the electric currents generated by the cells of the

gray matter would be facilitated. These lines of force would extend progressively, forming lines of communication from cell to cell within the brain and from the brain to the muscles and glands.

While such a facilitated pathway might be produced by the symmetrical arrangement of any electrolyte along the track of orientated chains of lipoid molecules it would appear that this may be one at least of the specific functions of potassium for the following reasons:— (1) Potassium is the only radio-active element in the body; (2) potassium even in chemical combination has the power of orientating and of maintaining the orientation of other ions, as in a crystal; (3) the potassium and lipoids in the body have a parallel distribution; (4) pursuant to the above considerations, it would appear that potassium is the element in the organism which has the most essential properties for organizing a system.

Zwaardemaker has made the following significant observation which if confirmed would relate the diffusibility of the potassium atoms to the radio-active property of potassium; and since, as we have stated, potassium is the only radio-active element normally present in living tissues, it would explain why we may consider that potassium rather than any other element is the one by means of which the nerve paths are generated. Zwaardemaker makes the statement that

"Where normal potassium, which is everywhere present, is concentrated in fixed combinations, as in the muscle tissues, it will permeate the whole surrounding tissue in all directions with its penetrating rays. In the immediate surrounding tissue only a few of the swift rays but many of the slow rays are absorbed. I feel that this continuous radiation working night and day, however weak it may be, provides a certain amount of energy which among other effects frees a small part of the atoms of potassium from their fixed combinations and releases them as diffusible potassium in solution. It is this free potassium which, when the permeability of the membrane is maintained, leaves the muscle cell and goes into the circulating fluid where we have found it in small amounts." [1]

In accordance with the generally recognized facts regarding potassium it would follow that each potassium ion projected

through the monomolecular lipoid membrane of a brain cell, would have the power of carrying with it and of orientating the ions of sodium, phosphorus and other electrolytes as well as the lipin molecules. In this way the nerve cells themselves could create from themselves a series of projections with a highly conductive property and it would follow that each of the infinite pathways in the white matter, having been thus constructed by the electric charges of the cells as the result of certain specific impulses conveyed to the cells, *would remain a specific conductor for the same type of electric discharge as that which created it.*

The white matter with its organization would then be the creature of the electric battery—the nerve cell. According to this conception, the white matter was not made first and the brain cells organized afterwards, but the brain cells themselves constructed the white matter by means of the creation of specific arrangements of potassium, sodium, phosphorus, the lipins and fatty acids in specific conducting paths, thus making the white matter a specific dynamic system. It is well known that the severed nerve fiber is recreated by the nerve cells. Thus the nerve cell may be said to secrete the nerve fiber, and in the same way the nerve cells may be said to secrete the white matter of the brain.

This conception is in accord with the observations of certain investigators regarding the distribution of potassium in living matter. Macallum, although he states that "it may also be regarded as certain that potassium does not subserve either the generation or conduction of nerve impulses" does draw the conclusion that "there is thus in living protoplasm a directing force controlling the distribution of potassium salts, a force apparently opposed to, or to express it with a due degree of caution, more refined than the ordinary physical force comprehended by the term osmosis."

By applying Macallum's method to the examination of nerve fibres for the presence of potassium, Macdonald found that "precipitates of potassium salts can be obtained at any point arbitrarily selected as the site of an injury" and contrary to the conclusions of Macallum, Macdonald believes on the basis of his own researches that potassium salts are "really present at

every point in the course of the nerve fiber, and that too in astonishing quantity."

"Let us then suppose that in all these events we have a modified representation of the process of excitation and its consequences upon neighboring segments of the fibre; a reversible change during which electrolytes are set free into a state of simple solution, and are then recovered from this state back into their original condition. Here truly there is the appearance and the withdrawal of a source of energy, a relay placed at every point of the nerve to ensure the continuous propagation of the excited state. Inorganic salts are set free to move; they move ever so little; the next segment of the fibre is charged as a consequence (let us say negatively); the colloidal state of the fibre is thus changed from its condition of equilibrium; as a result a setting free of electrolytes at this new point and the propagation of the process; in the meantime the communication of the negative charge to the onward segment has left the original segment positively charged, the state of colloidal equilibrium is thereby reproduced, and the last involved segment is brought to a condition of rest."

"Accepting all that is taken as known of the minute microscopical structure of nerve, there is no inherent improbability in the supposition that the inorganic salts of the nerve might be there held enchained in a highly concentrated solution free to move parallel, but not at right angles to and away from the fibrillae." [2]

and again in describing the potassium deposits in the granules which appear at the cut ends of the fibers and also in portions of the fibers remote from the site of injury, Macdonald makes the following statement:

"Such granules I have observed forming at the cut ends of the fibres, but also in portions of the fibres remote from positions of injury. Such granules may, even in portions of intact fibres, be observed to increase and again to diminish in size. They may be seen at any one time to be of different sizes and in different number in neighbouring portions of the axis-cylinder. There is, therefore, no temptation to consider them as permanent units of structure, and yet, after the admission of 'fixatives,' these very granules are joined together in lines to form neuro-fibrils. The granules not being permanent units of structure, it is therefore logical to con-

clude that the fibrils thus formed by their agglutination also are not permanent units of structure. The fibrils then may be said to be observed under conditions suggestive of artificial formation. This fact also has to be taken with the complementary fact, that artefacts of just this kind might be expected to appear within the nerve-fibre.

"Let us in illustration of this statement consider the possibility mainly dealt with in this paper, that the process of coagulation is attended with a sudden liberation of inorganic molecules, and therefore with a new condition of activity—molecular motion—around every centre of coagulation. It seems not unlikely that, in the extremely minute tubule of the nerve-fibre, this new activity, and the conditions of pressure occasioned by it, might systematise the spatial arrangement of these centres of activity along lines parallel to the long axis of the fibre. This being the case, there seems an ample basis for the opinion, that we should expect a symmetrical arrangement of lines of coagulated material. In fact given a sudden appearance of a uniformly distributed agency determining coagulation, we should expect the formation of 'neuro-fibrils' as a consequence of the energy changes accompanying this process."

"I have frequently watched the granular conditions I have described pass uninterruptedly through the nodes and have thus become convinced of the uninterrupted continuity of the axis-cylinder, and, therefore, of the absence of transverse membranes from these nodal points. This newly-described condition of 'pseudo-polarisation,' however, provides a complete explanation of the phenomenon of true longitudinal polarisation, just as it at the same time provides an explanation of the manner in which the electrolytes of the nerve may be set in motion in measurements of electrical conductivity, although usually locked up in its normal state of colloid solution." [2]

Pertinent to our conception that the actual generations of the nerve paths of action may be by the progressive deposition within orientated lipoid chains of potassium ions are the following observations of Macallum:

1. "In the spores of *Equisetum arvense* the cell which gives rise to the primary root hair is, from the first, very rich in potassium salts which, as the root hair begins to develop, collect at that point where the hair is to arise, and while the growth continues the inner surface of the hair membrane remains in association with the

salts. This appears to obtain also in the formation of the pollen tubes in *Lilium,* the potassium observed in the active cell of the grain appearing, when the tube develops, to accompany its extension downwards through the tissues of the capitate stigma. As the tube becomes very long the quantity of potassium that may be at any one point within its wall is very minute, or in traces only, but when the tube first begins to grow the amount at the point of growth is sufficient to make a clear demonstration of the fact."

FIG. 53.—Germinating spores of *Equisetum arvense,* (a) earlier, (b) later, stage. "In both the potassium seems to diffuse in advance of the cytoplasm which forms the primary root-hair." (× 250.) (From Macallum: On the distribution of potassium in animal and vegetable cells. *J. Physiol.* 1905, xxxii, 127.)

2. "In several preparations of *Spirogyra* which illustrated the process of conjugation there was found, within the tips of the outgrowing processes, and almost immediately adjacent to their terminal walls, a marked potassium reaction, quite distinct from, and much more marked than, that of the adjacent cytoplasm." [3] (Fig. 53.)

3. Macallum found also that potassium accumulates at the lumen border of cells during secretory activity, that is at the

border of the cell through which secretion takes place and that in the epithelium of the small intestine where the current goes in the opposite direction to that in the gland cells, the accumulation of potassium occurs at the portion of the cell next the basement membrane.[4]

Macdonald found that not only are potassium salts present at the site of an injury to a nerve but that they are "also discoverable in regions of the fibre distant from points of injury, provided that time is given for their appearance."

Macdonald makes the further and exceedingly significant suggestion that the Nissl granules in the nerve cells may be of the same "order of importance" as the granules observed by him in nerve fibers and at the severed end of the fibers. "Failing definite evidence upon which to make any assertion, it must at least be said that the well-known appearances accompanying 'chromatolysis' are extremely suggestive in character. They would seem to be the consequences of such changes in osmotic pressure as would result from the sudden liberation of salts into solution." [5]

In so far as the conscious operations of the mind are concerned these processes of progressive orientation of facilitated paths presumably begin with the birth of the individual. On this conception it is not difficult to understand why the nerve fibers find their way so inevitably from the brain to the muscle or gland. Electricity always travels from the positive to the negative pole; from the point or part of higher to the point or part of lower potential. Just as lightning travels from the clouds to the earth, so the current would pass from the brain toward the muscle or the gland with the final laying down of the facilitated pathway, the nerve fiber.

In like manner, just as the lightning may pass from cloud to cloud, that is, from a cloud of higher to a cloud of lower potential, so pathways may be formed from brain cell or group of brain cells to brain cell or group of brain cells. We can easily imagine that if the clouds contained the needed material and if there were a continuous electric strain between a stationary cloud and the earth or between a cloud of higher and a cloud of lower potential, in due time there would be constructed a conducting path corresponding to a nerve fiber from the cloud to

the earth. Moreover, this conducting path would be specific for the quality and quantity of current that created it. So within the brain the path created by the electric current instigated by the impingement of light rays on the retina would be specific for identical light rays; the facilitated path created by the electric current initiated by the impingement of sound waves upon the nerve endings in the ear would be specific for identical sound waves.

The following facts may be cited in support of this conception of the formation of facilitated pathways in the white matter of the brain which we conceive to be the foundation of mental processes.

1. There are no myelin sheaths in the white matter.

2. The white substance contains many neurofibrils which are apparently specialized paths.

3. As Cajal has shown, in certain parts of the brain in children from five days to a month old or in monkeys or rabbits some days old, it is possible to trace the entire length of certain of these fibers, the length of which becomes extended and their connections increasingly complicated as the age of the animal or individual increases. As he says: "the extension, the increase and the multiplication of appendices of the neurones is not otherwise arrested at birth but continues and nothing is more striking than the difference which exists between the newborn and the adult man from the point of view of the length and the number of the cellular ramifications of the second and the third order." [6]

4. As Cajal suggests, this hypothesis is strengthened by the fact that psychic as well as motor and sensory functions may be restored after grave lesions of the cortical centers.

Again to quote Cajal: "Such a return to the normal state forces one to admit the possibility that the healthy extremity of each of the disorganized cylinder axes grows, sends out new collaterals and transverses the affected regions, finally bringing dissociated neurones into contact. If the neurones themselves are destroyed, one would suppose that the new-formed cylinder axes would search out other nerve cells and enter into connection with them, thus giving a new direction to their activity. . . . If the faculty of growth of the neurones in the adult and their power of

creating new associations explains the capacity of man for adaptation and his aptitude for changing his ideological system, the arrest of activity in the neurones of an old man or of a man whose brain is immobile as the result of lack of instruction or for other reasons can in its turn make us understand the inimitable convictions, the lack of adaptability to the moral code and even the violence of the misanthrope. One can conceive equally that amnesia, lack of association of ideas, intellectual torpor, imbecility and dementia can be produced when, as the result of these more or less morbid conditions, the articulation between the neurones becomes relaxed, that is to say, when the expansions atrophy and cease to be in contact and the mnemonic spheres become partially disorganized. Our hypothesis also accounts for the more persistent conservation of old memories, of the memories of youth, in the old man, the amnesic and the demented, for the paths of association acquired a long time ago and exercised for many years have evidently acquired a great power in addition to the fact that they were formed at a period when the plasticity of the neurones attained its highest degree. . . . Other causes than those we have enumerated must undoubtedly play a part in this mechanism although today we are ignorant in what way. We may cite among them the morphological changes in the spongioplasm and the neurofibrils; the modification of the chemical constitution of the nerve cells; the more or less abundance of the neurones with short cylinder axes; the number and the variable position of the neuroglia cells in the gray matter and indeed certain other details, the whole nature of which we do not even suspect." [7]

As we have indicated before, Cajal's observations are throughout in accordance with the bipolar conception.

5. Lugaro, as cited by Cajal has attributed the creation of interneurone connections to the chemotactic phenomena which Cajal conceives explain the growth and articulation of the neurones in embryonal life. According to Lugaro, whatever may be its source, the nerve wave is always transmitted as the result of chemical phenomena. The external stimulations for example, according to Lugaro, provoke a chemical modification in the nerve endings, this modification in its turn acting as a physico-chemical excitant on the protoplasm of other neurones so that new nerve currents are created. He conceives that thus the conscious state itself would be due to chemical changes excited in the neurones by the sensory nerve terminations—

changes, the character of which would vary according to the termination.[8]

6. Tanzi, also cited by Cajal, conceived that the nerve current which passes most frequently across an articulation of neurones would arouse a more active nutrition in the articulated paths and in consequence a hypertrophy such as is shown in well exercised muscles. In the case of the nerve paths this hypertrophy is expressed by prolongation of the cellular ramifications, a prolongation which in turn diminishes the distance which separates the articular surfaces. According to this hypothesis, the conductibility of the nerve paths would therefore be increased since the resistance to the current would be in direct relation to the interarticular distance. In consequence, exercises which tend to diminish the intervals of articulation would be capable of increasing the functional power of the neurones. Cajal's comment upon this hypothesis is that it possesses the advantage of showing how habitual acts become easy and automatic as the result of repetition and how acts that we call conscious and voluntary as opposed to reflex acts are dependent in their physico-chemical phase on the state of resistance to the passage of the nerve waves.[8]

7. It would appear to be significant that the primary centers of memory are probably in the neighborhood of the centers of perception. Thus again to quote Cajal:

"All the mnemonic spheres thus far known to be present in man, that is, those of articulated language, of visual images, of words and of their auditory images, are found in the proximity of the corresponding perceptive center. Moreover, the common observation of many savants has placed the visual images in the external occipital cortex, that is, in close proximity to the center of visual perception. Finally the superior temporal cortical seat of the olfactory memory borders the center of olfactory perception. As for the secondary mnemonic centers their localization is interior. . . . It appears to us to be very probable that they are connected with all of the primary mnemonic centers of the two hemispheres by short fibers of association and by curved or callous fibers (corpus collosum) because of the necessity of connection between all the primary mnemonic centers throughout the whole cortex." [9]

8. Ross Harrison has shown that the axons are projected in nerve cultures [10] and it is well known that the axis cylinder degenerates when it is divided beyond the nerve cell.

9. In accord with the histological observations of Cajal and of Harrison is the fact that the most elemental lines of com-

FIG. 54.—Distribution of potassium in sensitive hair of Venus's fly-trap (Menten).

munication among paths of the nervous system are not established in a child for some days after birth.

10. Some years ago Dr. M. L. Menten in my laboratories, experimenting with the Venus's fly-trap was able by the use of microchemical stains for potassium to trace the course traveled by impulses from the sensitive hair to the effector mechanism.[11] This path consisted of a row of cells joined together end to end

A B

FIG. 55.—Parallel distribution of potassium and of fats in the leaf of Venus's fly-trap. A, section showing potassium: B, section showing fats. (Menten.)

and having a specific concentration of potassium along its course. (Fig. 54.) *These cells with their lipoid content and lipoid membranes and their specific potassium content constitute the nerve fiber and the brain of the fly-trap.* She demonstrated also that in the leaf of the fly-trap the lipoid substance had the same distribution as the potassium compounds. (Fig. 55.) In experiments with nerve fibers she demonstrated that in medullated nerve fibers, upon mechanical injury, upon electrical stimulation and under anesthesia, potassium was precipitated. That is, as the lipoids disappeared under the action of the lipoid solvent anesthetics, ether and chloroform, or as the result of injury, the potassium remained. The significance of this is that when the lipoids were destroyed by injury or by anesthetics, the facilitated paths along the fatty chains could no longer exist and nerve action was no longer possible. We assume that the electrolytes had facilitated the path and that the fatty molecules transmitted the nervous impulse.

11. Professor Marinesco has shown that oxidation ceases at the very border of the white matter, oxidation occurring only in the gray matter in the cells of the brain.[12] Thus lack of oxidation within this matrix where we conceive the facilitated pathways are orientated would leave the facilitated paths passive and undisturbed.

To summarize our conception regarding the application of the bipolar theory to mental processes, we consider that the white matter of the brain contains infinite numbers of chains of lipoid molecules containing potassium ions in a passive or resting position, each of the chains having been created by electric discharges from the brain cells. Conducting paths of every conceivable specificity have thus been created by infinitely varied arrangements of these infinitely small carbon or lipoid chains in the white matter of the brain and of the spinal cord. According to this conception, when these lines of specific static charge are "fired" by light waves, sound waves, contacts and so forth, they would become permanently orientated so as to offer a permanent conducting path from the nerve cells to the muscles and organs on the one hand, whereby muscular and glandular actions would be produced on the receipt of the specific stimulations, and on the other hand, between groups of brain cells

so that ideas, thought, and memories would be produced also on the receipt of the specific exciting stimulations.

This conception would explain the "organization" of the nervous system by activity, by training. According to this conception, memory, as we have indicated, would be seated in the facilitated portion of the lipoid molecules, some orientated into a complete "palisade" arrangement, some partly orientated, producing respectively strong and faint memories. (Cf. Mathews [13] and Troland.[14]) This conception would give a foundation for the lack of definite organization or arrangement of the white matrix as it appears under the microscope. It would explain the symmetric concentration of electrolyte along the connecting lines as shown in Dr. Menten's researches; it would explain the training of memory; it would explain the reason for the existence of the millions of nerve cells in the brain and cord, as only through the existence of millions of brain cells could the infinite memories, infinite responses, be made possible.

As to the nature of the specificity of the charge or action pattern passing over the conducting paths, changes in the frequency of vibration of electric charges and discharges have such well known values that it might well be an important factor in producing this specificity. Thus it is known that the conductivity of any medium at a frequency of 1000 cycles is very different from its conductivity at a frequency of 1,000,000 cycles. A high frequency current would readily pass over a path that a current of low frequency could not pass on account of polarization effects. Polarization causes increased resistance. Therefore one would suppose that one action pattern or line of force or specific conduction path could not be activated by one frequency and strength of current and readily also by another frequency and another strength of current. That is, the special senses would originate charges, the force and frequency of which are infinitely varied and for each charge certain conducting paths would be specifically attuned.

The electric currents, each passing over its specific path, would reach certain cells, the charges of which would in turn be "fired," the current therefrom in turn passing over facilitated paths and causing a specific response in a muscle or gland.

Or it might pass over a specific path to other brain cells, producing a memory of a previous like activation.

Thus an action or a memory or a thought may be produced by the physical energy of sight, hearing, taste, smell, touch or pain which in turn "fires" certain brain cells that in turn "fire" certain muscle cells or certain other brain cells, producing new ideas or awakening memories. And in turn these thought waves or new ideas or memories may also send a charge over facilitated pathways firing the same muscles, stimulating the same glands as those stimulated when the electric current which originally produced the facilitated pathway made its original impression.

From a superficial point of view this last type of action would be regarded as an act of will. Such terms as the "will," "judgment," "reflection," are but convenient terms for expressing what would appear in reality to be an intricate specific action of a cell or group of cells upon a cell or group of cells. Education and training, according to this conception, would be the effects of many mild or fewer stronger charges passing over constantly changing facilitated pathways.

In accordance with this conception, punishment, discipline, training, monomanias, broadmindedness, vocations—all the several qualities of "mind" would mean the sum of the potential in the brain cells plus the original quantity and quality of current brought to the brain cells by an external or an internal stimulus, plus the facilitated pathways, plus the millions of possible lines of force or specific conducting paths; a sum which may be conveniently expressed by the one term—"action patterns."

This conception then would explain the "organization" of the nervous system by activity and by training. It would explain why there are millions of nerve cells in the brain and the cord; it would explain the decussation of the nerves whereby the facilitation is doubled and both sides of the organism can be activated by a single impulse.

As Cajal says: "They (callous fibers) are not designed purely and simply to connect territories of the same name and of the same function in the two hemispheres. They have a more extensive rôle. They serve to establish a multiple and complex association, thanks to which every excitation born in the sensorial

spheres of one side is capable of exciting various centers on the opposite side." [15]

This conception would explain the lasting effect of deep impressions and the slight effect of lesser stimuli. It couples not only the nucleus and the cytoplasm of the cells into batteries but it couples the brain cells with the muscles and glands into batteries. It identifies the nerve cells as the positive—the muscles and glands as the negative elements of the battery. It supplies specific functions to the white matter of the brain and gives a reason for the communication between the brain and the muscles and organs on the one hand and between various brain cells on the other.

In accordance with this conception the difference between thought and muscular action would be that one is a reverberation of the stimuli in the brain and that in the other the charge runs down the nerve pathways to the muscles, the electric energy which keeps the circuits active in each case being furnished by the brain cells.

According to this conception when a given vibration enters the brain cells attuned to that vibration a given "thought" is produced or memory evoked just as when an electric wave reaches certain other groups, a gland or a muscle is activated.

By this conception memory and thought find their place in the universal bipolar pattern.

If there is not such a continuity as we have described between the seat of an external stimulus and memory of that stimulus or the course of thought which it instigates, then one must suppose that some external force or agency intervenes between the receipt of the external stimulus and the resultant memory, thought or muscular action. In motor plants such as Venus's fly-trap the contact of an insect is the external stimulus which sets in motion forces which result in the closing of the leaf trap. The sequence in this case is obvious and no one would venture to suggest the intervention of a supernatural agency. Many unicellular organisms respond to the stimuli of light, heat, chemical agents, translating stimuli thus received to action without the mediation of any supernatural agency and without a nervous system.

In a higher animal which has been deprived of its brain, a stimulus is transmitted up the nerves to the spinal cord with the resultant reflex action from the ganglia of the cord, as a result of which the muscles are activated. If in such a brainless animal, a group of cells were added that would first stimulate each other before the ganglia of the cells whose discharge produces the action is effected, this intervening group of nerve cells would be in effect a brain and this is just what we conceive the brain to be—a group of intervening cells adapted to receive and translate into final action finer impulses with a more exquisite distinction than the ganglia of the spinal cord or the receptive organs of brainless organisms can achieve.

In accordance with this conception therefore, we believe that starting from infancy, parents, companions, the natural forces of the environment, teachers—all the infinite elements of the experience of life are creating in the brain matrix with its infinite capacity, an infinite number of action patterns which make up the changing personality of the individual—a personality which changes with every stimulus until final equilibrium or death ends the life of the individual.

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CHAPTER X

A Suggested Application of the Bipolar Theory to the Processes of Reproduction and to the Transmission of Acquired Characteristics—Heredity

If the bipolar theory is to stand it must not only show a general plan of evolution from the original unicellular organism to the complex, multicellular organisms of the higher animals and man, but it must explain the mechanism of cell division upon which depends not only the evolution from unicellular to multicellular organisms but also the development of each multicellular organism from the single cell—the sperm, the ovum. It must account also for the variations and identities which constitute the physical characteristics of each individual; that is, it must explain how the physical characteristics of parents are transmitted to the offspring.

While we must, of course, acknowledge our inability to supply solutions for these problems, nevertheless the following suggestions are offered as indicating the possible rôle of electric energy in processes of reproduction.

It should be considered first of all that no living organism is static either in size or in function. According to our conception, life itself is due to a state of unbalance between the positive and negative elements in the protoplasm. The primary result of this state of unbalance within a cell, whether that cell be a separate organism—a protozoan, or a constituent part of a multicellular organism, is the initiation of processes of growth. According to our conception, life itself is due to the positive and negative electrical elements of protoplasm.

We may assume that since the nucleus is the kinetic center of activity, it would increase in size and electric potential at a higher rate than does the cytoplasm. Since the nuclear contents have an identical sign of charge, there would be a tendency for the nuclear contents to repel each other and divide into two

centers of activity each possessing a like sign of charge. Since the kinetic forces of the nucleus are greater than those of the cytoplasm, these repellent forces within the nucleus would finally be sufficiently strong to cause a complete division of the nuclear substance. Once this division has been accomplished a reverse situation would hold and the forces within the small "daughter" cells would then be greater than the intranuclear forces with the result that a similar process would take place in the cell as a whole; one portion of the cell with its small nucleus repelling the other side of the cell with its small nucleus until the repulsion of the like signs of charge in the cytoplasm would cause a complete division into two cells.

In the unicellular organism this repulsion between like signs of charge would be sufficient to cause a complete disruption of the cells. We may imagine that at some time the repulsion between these intracellular forces was not sufficient to cause a complete separation of the cells so that the cells remained in contact but divided, thus causing a bicellular organism. And even before this took place one can understand how the forces within the cytoplasm were not sufficient to cause a disruption into two cells after the nuclei had divided, so that a binuclear organism would be formed.

Once the process of division into two cells had been started, this electrical law, that forces of like electric charge repel each other, would continue to operate by successive cell divisions.

That electrical forces are concerned in the processes of cell division is no new conception. The close resemblance of the mitotic figures and of the amphiasters to magnetic lines of force has long been appreciated. This resemblance is so striking that it has been imitated by Lillie and others by means of magnetic models. It has been objected to this conception that "attempts to influence the mitotic field by causing cells to divide in the magnetic or electrical field . . . have failed." This would not appear to be a valid objection because we may consider that in common with what we conceive to be the laws governing the phenomena of life, these phenomena are produced only in response to specific electric forces just as the receptive mechanism of a radio apparatus responds only to specific wave lengths. It is not strange, therefore, that the application of

electrical and magnetic influences might fail to cause a cell to respond in the same manner as it responds to forces to which it has been attuned in the process of its own development or that of its ancestors.

Many other objections to the conception that the processes of cell division are electrical processes have been advanced. The elaborate appearance of the mitotic figures under the microscope have suggested equally elaborate conceptions as to the combinations of processes which are involved; and these intricate conceptions have given rise to equally elaborate descriptive terms.

We do not presume even to attempt to identify the electrical origin and development of each stage in the process of cell division. We do assume, however, that fundamentally, cell division is amenable to the law of bipolarity which, we believe, is the basis for all living processes.

Among the facts which might be cited in support of the conceptions outlined above is the variation in the development of fresh water algæ whereby cytoplasmic division may be modified.

"By exposing the normal forms to lowered temperature, and in certain other ways, it was found that mitotic division may be so modified that although the chromosomes divide the daughter-nuclei do not separate normally and cytoplasmic division fails. Binucleate cells are thus produced, the two nuclei either remaining separate or fusing into one, which then grows to twice the normal size. In either of these cases the doubling of the nuclear mass is followed by growth of the cytosome to double the normal volume; and by the continued division of such cells are produced giant filaments which may be reared to maturity, produce gametes of double the normal size, and conjugate to produce correspondingly enlarged zygotes." (Wilson.) [1]

Another supporting fact is "the undoubted causal relation between nuclear volume and cytoplasmic growth, i.e., the *Karyoplasmic ratio* of R. Hertwig," to which Wilson alludes as "a fact of great theoretical interest."

Not only the primary cell divisions but also the permanent interrelations of the cells must be related to the bipolar concep-

tion. In the higher animals these intercellular relations are principally maintained in the ramifications of the nervous system; in the lower animals these interrelations are probably accomplished by means of the strands of protoplasm. Such connections are well known in many of the simplest plant forms. They exist also in certain animal tissues which are not provided with nerve fibers such as cartilage and bone.

"Plasmodesms or cell-bridges are of general occurrence in the epithelial tissues, where they were first observed in epidermal

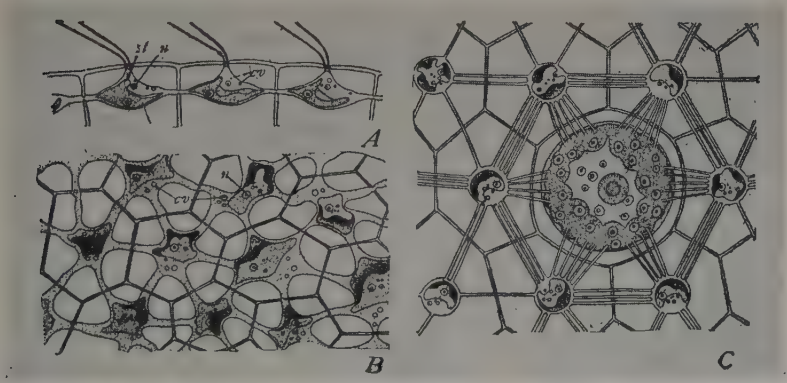

FIG. 56.—Protoplasmic cell-connections (plasmodesms), in *Volvox*, somewhat schematized (*Janet*). (From Wilson: The Cell in Development and Heredity, New York, 1925, p. 103.)

'spine-cells' ('Stachelzellen') and supposed to be spine-like processes from the membrane or cell-periphery (M. Schultze, 1864). Later studies by many observers (Ranvier, Renaut, Pfitzner, Schridde, Kromayer, Cajal, etc.) proved these structures to be protoplasmic inter-cellular bridges, and further showed that they are traversed by fibrillae, which may be followed from one cell to another and even through several cells. The plasma-bridges have since been found in the columnar epithelia generally. Further, it has been shown by a considerable number of observers that the germ-cells in both animals and plants may be connected with the surrounding somatic cells (follicle cells, etc.) by protoplasmic bridges. Plasma-bridges have also been described in the case of embryonic cells of many types and considerable evidence has been produced to show that they may here play an important part in maintaining the unity of the organism.

"The facts thus briefly reviewed have led some important modern

writers to accept Heitzmann's general conclusion almost in its entirety. A. Meyer, for example, expresses the opinion that both the plant and the animal individual is a continuous mass of protoplasm that forms a morphological unit whether it appear in the form of a single cell, a multinucleated cell, or a system of cells." (Wilson.) [2] (Figs. 56-58.)

It would seem probable that the universal presence of these conducting connections between cells would maintain electrical

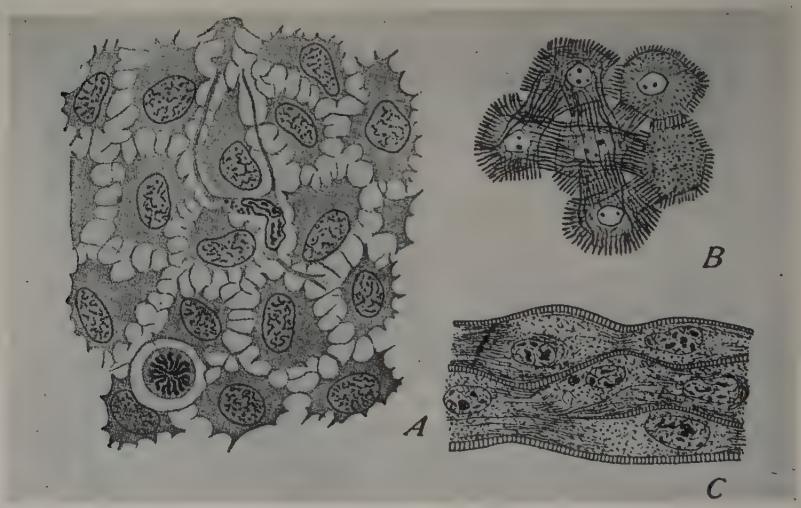

FIG. 57.—Intercellular bridges (plasmodesms) in animal tissues (*A, Flemming; B, Rio-Hortega; C, Ide*). *A*, epithelium of the gill-lamellæ of salamander-larvæ, deeper layers in horizontal view; *B*, cells from the mucous membrane of a nasal polypus, fibrillæ traversing the inter-cellular bridges; *C*, human cancer-cells. (From Wilson: The Cell in Development and Heredity, New York, 1925, p. 105.)

equilibrium among groups of cells and that, therefore, when they were broken by injury or chronic irritation this equilibrium would be destroyed with resultant comparative freedom of growth within one or another group of cells thus producing an unlimited growth among them (cancer). This would account for the apparent similarity between neoplasms in vegetable and in animal organisms and for the fact that in the production of each, chronic irritation plays an important rôle.

The symmetry of growth along axial planes would appear to be related to the fundamental polarity of living cells in every stage from the unicellular organisms to man.

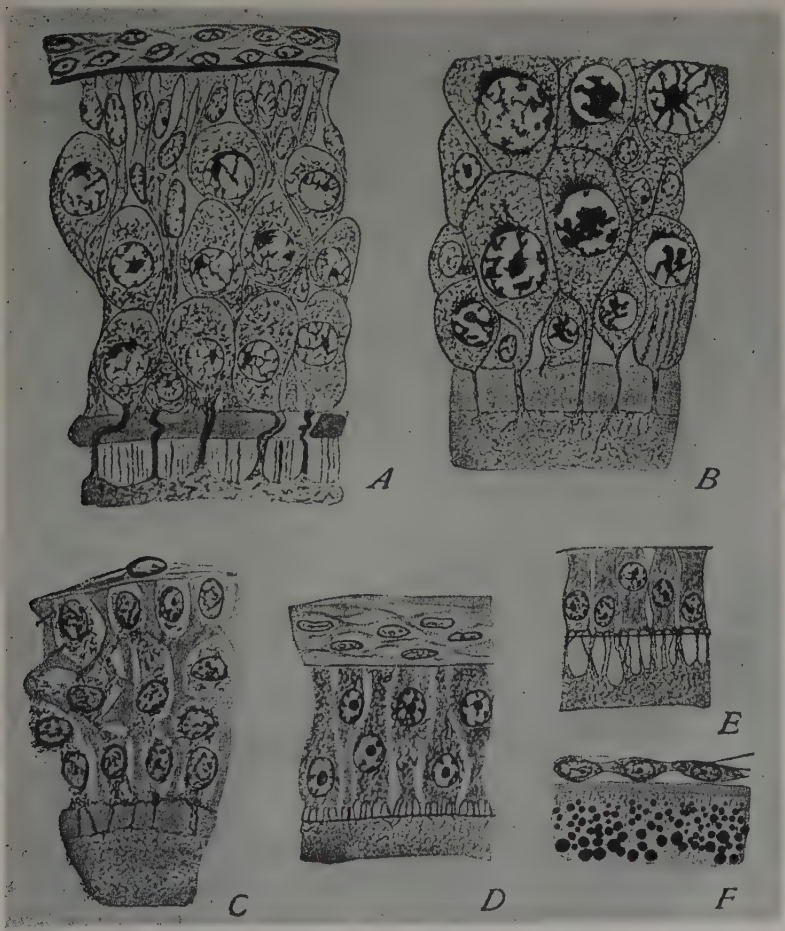

FIG. 58.—Connections between oöcyte and follicle-cells in vertebrates (*Retzius*). *A*, in *Chimaera; B*, *Raja; C*, the rabbit; *D*, the pigeon; *E*, the domestic fowl. The foregoing from earlier stages of the oöcyte; *F*, late stage in *Lacerta*. (From Wilson: The Cell in Development and Heredity, New York, 1925, p. 337.)

"Child has recently emphasized the general importance of 'metabolic gradients' as an expression (if not the actual cause) of func-

tional polarity, which in his view may sometimes be merely a graded difference in the rate of metabolism in the direction of the axis (though it may often be more than this). In support of this he has proved experimentally, by a study of susceptibility to the action of poisons and narcotics, that such gradients undoubtedly exist in the direction of the main axes, both in organisms as a whole and in individual cells.

"Interesting possibilities for the further analysis of physiological polarity are opened by recent experiments. It has been shown that in hydroids the oral region is electronegative as compared with the basal; and also that axial differences of electrical potential similar in type, though different in detail, exist in other animals; and Lund has demonstrated that in the alga *Fucus* the polarity of the eggs shows a distinct orientation with respect to the electric field. Hyman and Bellamy emphasize the fact that in the various cases studied by them the electrical gradients closely correspond with the metabolic, levels of high metabolic rate being electronegative to those of lower." (Wilson.) [3]

That the nucleus is a primary agent in the constructive processes of cytoplasmic growth culminating in cell division is well recognized. Whatever may be the rôle of the chromosomes in the processes of reproduction, it is known that they bear direct relation to nuclear size. Wilson and others have called attention to the

"remarkable contrast between nucleated and non-nucleated cell-fragments in respect to synthetic processes. The earliest observations on this subject were the classical ones of Waller (1852) on the regeneration of nerve-fibers, which proved that this process only takes place when the axis-cylinders remain in connection with the nucleated cytosomes of the nerve-cells. When a nerve-fiber is severed the distal portion degenerates, while the proximal portion (still connected with the nerve-cell and its nucleus) may readily grow forth until the missing portion is restored. This observation, repeatedly confirmed by later observers, was not wholly decisive, but nevertheless gave the first clear indication of the necessity of the nucleus for growth, regeneration and differentiation." [4]

Moreover, if we are correct in our assumption that cell activities—function, growth, division—are due to a difference in potential between the nucleus and the cell body, it is certainly

significant that, as has been observed by Conklin in studies of the life phenomena of Crepidula, "the largest nuclei appear in blastomeres that contain the largest amount of active protoplasm, irrespective of their total size." [5] (Fig. 59.) This is well shown in the accompanying cuts in which it will be seen that the largest nuclei are in the smallest cells and as we have already stated in another chapter, this variation in nuclear

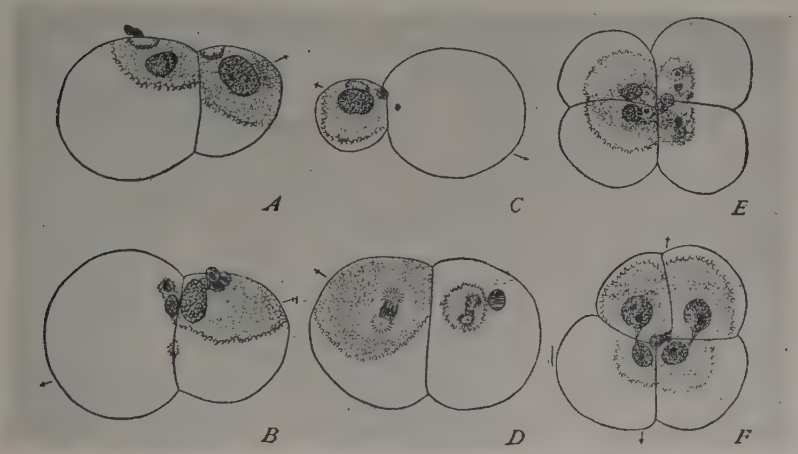

FIG. 59.—Karyoplasmic relation in segmenting eggs of *Crepidula* after centrifuging. Direction of the centrifugal force shown by arrows (*Conklin*). In each of these 2-cell and 4-cell stages the nuclear size is proportional to the amount of active protoplasm (stippled), not to that of the cell as a whole. (From Wilson: The Cell in Development and Heredity, New York, 1925, p. 732.)

plasma ratio in its relation to the rapidity of growth and reproduction of cells is strikingly manifested in cancer cells.

Wilson calls attention also to a fact which is of striking significance in its application to the bipolar theory.

"It is now rather generally accepted that the more primitive types of cells were very probably devoid of an *individualized* nucleus, i.e., that the nuclear materials were originally scattered through the cell in the form of chromidia-like bodies which only at a later period became aggregated to form a nucleus of the ordinary massive or vesicular type. This view finds its support in the present existence of various forms among the Protista in which the

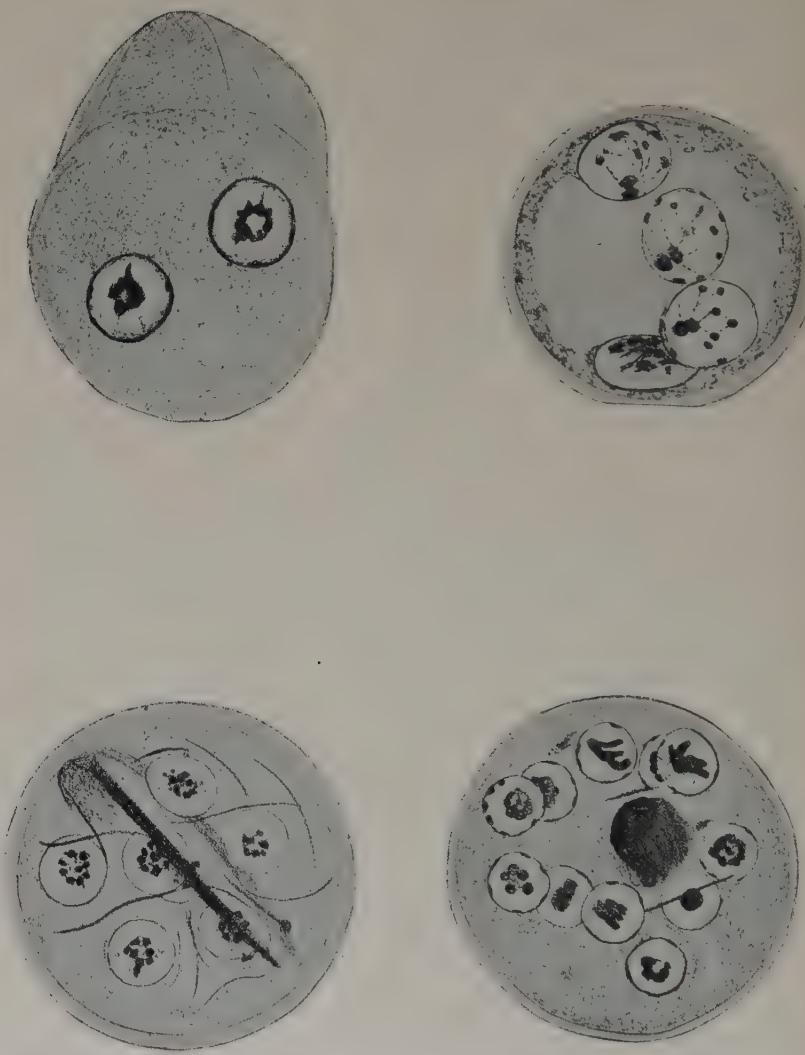

FIG. 60.—Two-, four-, eight-, and eleven-nucleate phases of *Councilmania Lafleuri*—a parasite of the human intestine. (From Kofoid and Swezy: Univ. Calif. Publ. Zoöl., 1921, Vol. 20, pp. 169-198.)

nuclear material is actually thus distributed through the cell, and by the fact (if existing accounts are correct) that in some of these forms individualized nuclei may arise either by enlargement of the

individual chromidia or by their aggregation into a granular mass, in the processes of gamete-formation, mitosis, or spore-formation (bacteria)." [6]

Such examples as these might be multiplied by anyone who will review the phenomena of growth and of cell division in the protozoa as they are described by Conklin, Hertwig and a multitude of other observers and cannot fail to be impressed by the extent to which each process may be explained by the bipolar theory.

It remains to offer a suggestion as to the possible manner in which the characteristics of the parent cells or of the parent aggregation of cells is impressed upon the new cell or on the descendent aggregation of cells. In accordance with the bipolar theory the nucleus of the original unicellular organism—the positive pole, was the prototype of the brain and central nervous system of the multicellular organisms. As we have noted above, the unicellular organism cannot function without the nucleus. It is the dynamic center, the control center, the organizing center. If the nucleus is removed from a unicellular organism it ceases to function and cannot reproduce itself. We must conceive therefore that in the nucleus of the ovum must reside those potential qualities which are to govern its later activities.

In the unfertilized ovum the nucleus is balanced by the cytoplasm, hence exerts no influence upon it. As soon, however, as the nucleus of the ovum is reinforced by the nuclear spermatazoön of the male a difference of potential is established which becomes at once effective in the initiation of the processes of cell division and differentiation by means of which the new individual is constructed.

These premises, however, do not explain how the reinforced nucleus of the ovum can construct out of the apparently unorganized cytoplasm of the ovum and its own structure, a new individual resembling its parents. It must be presumed that there exists in the cytoplasm and in the nucleus the physical antecedents of the structures and parts of the fully developed organism. Just as in many unicellular organisms, projections from the nuclear structure appear to have definite neuromotor

functions, and parts of the cytoplasm are differentiated to perform the functions respectively of ingestion, digestion and elimination, so we may consider that in the cytoplasm and the nucleus may be found in miniature the organs and tissues of varying functions in the developed individual. Moreover, in the fertilized ovum are at once initiated electrical currents between the nucleus and the cytoplasm, by means of which the rudiments of the muscles, glands and viscera begin to be organized, electric currents which differ not at all from those which accomplish the further growth and development of the child after birth.

I can do no better in this connection than to quote again Wilson's summary of the point of view of various investigators, with Wilson's own comments thereupon.

"To Bonnet and other preformationists the localization problem offered no difficulties. The Gordian knot was cut by the assumption that the embryo is from the first preformed in the egg. The final overthrow of this doctrine by Wolff and his successors excluded this easy solution, but the possibility still remained that the egg may contain prelocalized regions that are inevitably predestined for the parts to which they give rise—to a certain extent such predestination is indeed a matter of observation in the case of eggs that visibly display polarity and bilaterality. The questions here raised were discussed by Wilhelm His ('74) in his interesting work *Unsere Körperform*. 'It is clear, on the one hand,' he says, 'that every point in the embryonic region of the blastoderm (of the chick) must represent a later organ or part of an organ, and, on the other hand, that every organ developed from the blastoderm has its preformed germ (*vorgebildete Anlage*) in a definitely located region of the germ-disc. . . . The material of the germ is already present in the flat germ-disc (in the chick), but is not yet morphologically marked off and hence not directly recognizable. But by following the development backwards we may determine the location of every such germ, even at a period when the morphological differentiation is incomplete or before it occurs; logically, indeed, we must extend this process back to the fertilized or even the unfertilized egg. According to this principle, the germ-disc contains the organ-germs spread out in a flat plate, and, conversely, every point of the germ-disc reappears in a later organ; I call this the *principle of organ-forming germ-re-*

gions.' Ray Lankester ('77) developed this conception as follows: 'Though the substance of a cell may appear homogeneous under the most powerful microscope, it is quite possible, indeed certain, that it may contain, *already formed and individualized,* various kinds of physiological molecules. The visible process of segregation is only the sequel of a differentiation already established and not visible.' The egg-cytoplasm has a definite molecular organization directly handed down from the parent; cleavage sunders the various 'physiological molecules' and isolates them in particular cells. Whitman expresses a similar thought in his classical work on *Clepsine:* 'While we cannot say that the embryo is predelineated, we can say that it is predetermined. The "histogenetic sundering" of embryonic elements begins with the cleavage, and every step in the process bears a definite and invariable relation to antecedent and subsequent steps.' . . . The conclusion of Rabl ('79) was similar: 'In spite of ourselves the question is forced upon us whether we must not assume the existence, even in the unsegmented egg, of a quite definite and orderly grouping and distribution of the protoplasmic particles and molecules.' Van Beneden ('84) pointed out the close kinship of this conception to that of a theory of preformation: 'If this were the case (i.e., if the egg-axis coincided with the principal axis of the adult body), the old theory of evolution would not be as baseless as we think today. The fact that in the ascidians, and probably in other bilateral animals, the median plane of the body of the future animal is marked out from the beginning of cleavage, fully justifies the hypothesis that the materials destined to form the right side of the body are situated in one of the lateral hemispheres of the egg, while the left hemisphere gives rise to all of the organs of the left half.'

"Later researches, both comparative and experimental, have brought forward a complete demonstration of the essential correctness of these conclusions. Many cases have now been made known in which the egg-substance is more or less definitely marked out—by the presence of pigment, specific types of granules and the like—into visibly different areas which give rise to particular parts of the embryo; and artificial destruction or removal of these areas is followed by the formation of an embryo from which the corresponding parts are absent or defective." [7]

It is no more logical to conclude that every organ and tissue in the adult animal has not its physical, specific material in the

nucleus and cytoplasm of the fertilized ovum than to say that the metal and wood and fabric in the automobile shop had no previous existence but appeared *de novo* in the finished motor car.

We have stated in a preceding chapter the conception that within the brain and central nervous system of the individual have been laid down facilitated paths, each of which responds specifically to specific vibrations transmitted to it by certain stimuli. And these specific vibrations when conveyed to the muscles or glands or viscera excite in them specific vibrations resulting in specific action. In view of the theories outlined above and our own conception, is it not reasonable to assume that in the sex cells of the parents specific vibrations are developed for each of the infinitesimal differentiated portions from which the differentiated organism is to develop.

Thus each organ of a plant or of an animal may be regarded as a separate species, and as such must furnish the specific energy to reproduce itself in the seed, just as if the organ were leading a separate existence and reproducing itself as simpler organisms do. Sex organs have the ability to affect profoundly certain other organs of the body, such as, for example, the brain, the thyroid, the adrenals, etc. If the diminutive cells of the sex organs can exert major influences on distant powerful organs, one would suppose the reverse would be true, and that each organ must exert a distinct influence upon the cells of the sex organs.

The manner in which this influence may be developed may be hypothecated as follows:—The dynamic units forming protoplasm are the progenitors of the cells constructed on a similar pattern which form the organs which in turn form the larger organisms. Among the protoplasmic bipolar units a closer communication exists than among the organs of the larger animals and plants. And again the separation of the chemical constituents of the protoplasmic units is greater than the separation of the same chemical elements in non-living matter. Living matter is held together in electric systems which are more loosely bound together than in non-living matter, thus making possible the accumulation of charges—the development of internal strain until the dividing point is reached and identical

new units are formed as the result of electric repulsion. These we believe are the pangens of De Vries which he considers to be the bearers of the hereditary characters. These protoplasmic units are constructed on the universal pattern of energy found in all the non-living and as we believe in all the living.

Owing to their loose bonds these primary bipolar units are readily thrown out of equilibrium, and hence their size and character are readily changed. Such loosely balanced physical units having such easily disturbed equilibrium could be easily modified by physical forces, especially by any specific electric vibratory force. Thus the dominant electrical units of the plant or animal might exert their characteristic influences on this sensitive physical unit through the mediation of specific electric forces. In growth and in repair, these specific electric forces would apparently build up all the characteristic structures including the protoplasm within the cells, this protoplasm containing the physical dynamic units. It may be argued that growth and repair come from the contiguous protoplasm and that cells do not play a rôle, but in the case of divided nerves, or in the case of separation of the nucleus from its protoplasm, provided communication be maintained by a conducting strand, it is obvious that the specific energy that sustains and that repairs the detached protoplasm is furnished by the cell. It does not seem difficult to conceive that there may well be an analogous transference of specific energy from any parent plant or animal to the protoplasmic units—pangens (De Vries), physiological units (Spencer)—in the sex cells.

An important point in our conception is that what is inherited is the *pattern of energy,* not the chemical elements of the parent. The atoms and molecules of the chemical elements in the developing plant or animal are the building stones which are used by the energy of the primary physical unit. From identical atoms and molecules, therefore, this primary energy mechanism will build identical forms. If by the application of another form of specific energy than that by which it was created the physical structure of this labile unit is altered, a corresponding change in the related characteristics of the new individual will be carried on.

The demand for a physical basis for heredity was recognized by Darwin in his pangenesis theory, and by the conceptions of Weissman, Naegeli, De Vries and Spencer, respectively of "ancestral plasm," "idioplasm," "pangens," and "physiological units." In all these conceptions, however, the purpose was to supply a form and structure as the fundamental basis of heredity. In our conception, on the other hand, specific energy is the fundamental basis, and form and structure are the products and tools of that specific energy. For if living organisms are energy transformers, it would seem logical that *the primary rôle should be played by energy* and the secondary by form and structure. This hypothesis does not contradict Darwin's theory of pangenesis, but it offers a possible explanation of that theory. Darwin's theory assumes that the cells of the organism each contribute a small gemmule larger than a chemical molecule but smaller than the smallest organism. To Darwin's mind it was logical to conceive that each cell must make a hereditary contribution to the sex cell. According to our conception instead of contributing a particle of material to the sex cells, the cells of the body construct the element in the sex cells at a distance by the specific energies of cells or cell groups, thus satisfying the logical requirements of Darwin's pangenesis for the transportation of gemmules from somatic cell to sex cell. Darwin supposed that the gemmules thus transported to the sex cells would assimilate food and divide; but so could such a physical unit as we hypothecate. We may also logically assume that these specific energy units may remain dormant for generations, until other competing units, which dominate for a time, in turn allow them to dominate. The physical balance which determines which type of primary unit will predominate may depend on the energy of the synergistic units. A unit may be represented in a sex cell and yet may not dominate the type of structure or of energy, just as in some lower forms a part of the animal may grow into a whole animal only when the dynamic preponderance of the whole animal is removed. Also it may be possible that the chance reinforcement of equal energy forms may give predominance in the medley of chances in breeding. Thus this energy theory of heredity indicates how pure breeds reinforce and mixed breeds counterbalance and

hence reduce the whole energy effect, thus suggesting a physical reason for the weakness of hybrids.

It remains to consider by what mechanism the perpetuation of general form-species may be effected. It may be supposed that through long use—for eons of time—the dynamic units of force or energy transformation have become stabilized and static so that they cannot be modified by ontogenetic energies that are constantly developed in each generation. On the other hand, the energy units the activities of which created the ancestral forms, now have the power of creating the high spots only; e.g., although the human embryo passes through the stage of a fish, it only shows, as it were, a fish gesture. The form, the tail and fins, the shape of the head, the eyes, the scales, the psychic characteristics of a fish never appear. The fish stage and all the other stages of the ancestors are mere pale shadows of the past and do not represent any organ of the bygone species that could perform an ancient function. At no time could a human embryo break off its progress toward becoming a human and become a fish. The phylogenetic remnants of species repeated in the human may not represent a complete roster of his predecessors, as many ancient forms may have been left behind altogether. In other words, the energy units of ancient forms could assimilate food, could grow and could reproduce only while the more labile hence more powerful energy transforming units of the more recent forms were gaining the ascendency; and when that ascendency was achieved the later units of energy outstripped the older units in acquiring and transforming energy and consequently the ancient units remained passive or regressed. The ancient or phylogenetic units, therefore, may serve no useful purpose, just as such vestiginous organs as the muscles of the ear of man do not serve any useful purpose; but have been outstripped by their competitors for food and energy. The struggle for existence would bring about the elimination of such ancestral development, for if a human embryo developed into too much of a fish it could not become much of a man and hence would lose in the struggle for existence. The embryo may be said to make use of the energy principle of the ancestral forms just as the modern ocean liner makes use of the energy principle of Ful-

ton's steamboat, but does not continue the structure of the latter. It may be questioned whether the human embryo requires the ancestral contribution any more than the human organism requires the vestiginal muscles of the ear, requires the appendix vermiformis, or than the occasional horse requires the faint zebra stripes. The phylogenetic structures like the vestiginal may have historical value only.

To suppose that the speed of growth of the human factors in the growth of the human embryo at the fish stage for example, is due to stimuli from the outside is to overlook the fact that outside stimuli are not available to the fetus *in utero*. That the human development predominates must mean rather that the energy units representing the human must outnumber greatly the energy units representing the fish. In consequence the human elements which play upon each other and reciprocally increase each other's speed of growth will overcome the energy units of the fish. Hence, the human organism can grow unhindered by the competing weaker fish units.

If it were possible that the embryo of man were to have taken from it every element except the energy elements of the fish, would a fish then be born? It is more probable that the fish and other phylogenetic elements show man to carry still vestiges which in time will be eliminated, but which are not necessary to the development of man. For would one suppose that if the elements in the ovum of man characteristic of the fish were removed that the ovum then could not develop man?

That the energy units in the sex cells are exceptionally labile is indicated by the fact that they show a greater susceptibility to radiation than do somatic cells. The looser the bonds in energy systems the more readily is their equilibrium disturbed and in consequence the greater is their power of energy transformation and hence of function and growth. If one unit of energy of an embryo outgrows another it indicates that the former is a system of looser bonds; that is, a system which is more easily influenced—has more power of growth. Thus we may suppose that the energy units of the ancestral forms become progressively more stable and hence less able to compete with the later more mobile units. This relative passivity of the ancient units limits their power of growth. We may suppose

that this same principle would apply to the inheritance of more recently acquired characteristics. Thus the characteristics of a child would depend upon the relative labilities of specific energy units transmitted to it from its immediate and more remote ancestors. This would explain the occasional "throw-backs" to remote ancestral appearances. Thus when two specific energy units, one from the mother, one from the father—compete in forming a given feature of the child and that of the mother gains ascendency and so creates the feature, it does not necessarily mean that the paternal unit is destroyed; it may remain inactive, potential, to reappear in another generation.

"It is known that when the antennae of a snail, the chelae of a crab, the feet of a salamander or the head of a worm are amputated, these organs are reproduced even when the amputation is performed during adult life.

"Spallanzani has cut the feet and tail off the same salamander six successive times, and Bonnett seven times, and each time feet were reproduced of exactly the same size as the former ones without any increase or decrease in any part. These facts show that the formative agent, whatever it may be, is always external to the part formed, and that it exercises upon the whole development of that part and throughout its entire duration a continuous action, and further that it remains itself unaltered even after the completion of its work and consequently is capable of renewing it at every favorable opportunity." [8]

According to our theory the new formation is the result of the action of the specific energies of the cells that originally played the dominant rôle in forming them. We may suppose that the reconstruction of the amputated organs is due to the building power of the energy units which remain. Thus when certain parts of the structure of an animal are destroyed, repair is due to the electric strain or unbalance which is then established. The growth of organs and parts ceases when the stage of dynamic equilibrium is reached; the removal of a part upsets equilibrium, and hence growth proceeds until equilibrium is again established. It must be assumed that the reproduction of severed parts in less differentiated forms is along the lines of original growth, and that the first cells formed were probably

of a lower order than the later more highly differentiated cells. We may suppose that cells can form cells of the same or of lower types but never higher types of cells, just as the nucleus can organize cytoplasm but cytoplasm cannot organize a nucleus.

We may conclude then that "regeneration is nothing else than a particular case of generation or reproduction and that the nature of one is substantially identical with that of the other; for, to use the words of Delage, 'generation is only the regeneration of a complete organism by a portion of greater or less size attached to it or detached from it'; so the causes of the regeneration, for instance, of a little disc of skin which has been renewed must be essentially the same as those which effect a complete reproduction." [9]

If the removal of one testicle or one mammary gland during development is followed by an enlargement of the other, it indicates that forces at a distance are capable of controlling their growth—i.e., the organism has a quota of specific energy which may be drawn upon selectively. If this is true in the case of the partially developed organism, may there not be a quota of specific energy which may be drawn upon selectively to organize the "amorphous" testicle or ovary in the sex cells? And in like manner one would suppose that each essential organ or tissue has a quota or ratio of specific energy, the exercise of which controls corresponding elements in the sex cells.

When a unicellular organism is divided in such a manner that each part includes portions of the nucleus and of the cytoplasm, the nuclear fragments will organize new individuals. In like manner the nuclei of the sex cells may organize the cytoplasmic part into an organism in which the nucleus becomes the nervous system and continues to govern the organized cytoplasmic portions. This point of view is not discordant with that of many investigators. Thus Cope makes the statement that heredity may be considered as "the transmission of a special energy from a point of stimulus to the germ cells, and its composition there with the emphytogenetic (inherited) energy into bathmism (or evolutionary energy)" [10]; and Rignano adds:—"From this he (Cope) at once draws the conclusion that as soon as a new character is acquired by the soma in consequence of a definite stimulus, it appears at the same time in the germ-plasm also." [11]

"We may compare the building of the embryo to the unfolding of a record or memory which is stored in the central nervous system of the parent and impressed in greater or less part on the germ-plasm during its construction, in the order in which it was stored. This record may be supposed to be woven into the texture of every organic cell and to be destroyed by specialization in modified cells in proportion as they are incapable of reproducing anything but themselves." [12]

If for germ-plasm we substitute specific energy pattern, this conception would apply to our own thesis. Another illustration by Rignano is especially pertinent to our conception:

"Finally a number of organs which would attain their complete development through the ontogenetic stimulus alone, have their development hastened by the accidental intervention before the proper time of the requisite functional stimulus. Thus, for example, in prematurely born children the visual sense develops earlier; that is to say, its development is accomplished in a total number of days, counting from the first instant of development, that is smaller than the ordinary number such as would be given by the time of ordinary gestation augmented by the number of days necessary for the infant born at term to acquire the same degree of development of sight. And this demonstrates again, that the functional stimulus can replace the ontogenetic stimulus, or better that it can coöperate with it and add itself to it, thus strengthening its effect; a thing which would be difficult to conceive of were the two stimuli of different nature." [13]

That energy from a distance can organize elements in equilibrium into energy transforming mechanisms is shown by the fact that the simplest unicellular organisms are organized by the energy of the sun's rays. The whole organic world has been and is being organized by energy transmitted from the distance of the sun. Surely then the sun's energy released within an animal may be capable of organizing energy systems in every part of the organism including the sex cells. When a rose or an apple tree is grafted the graft will produce a flower or fruit after its own kind and unlike the flower or the fruit of the bush or tree in which the graft was implanted. But the tree which in turn grows from the seed of the flower or fruit of the graft will in turn produce not the apple or rose of the

graft, but an apple or rose like the tree or bush in which the graft was implanted. Why did the seed from the fruit of the graft not produce a tree whose fruit was like its own fruit? It could only be because influences from the remainder of the tree sent organizing energy into the bud and fruit of the graft creating a miniature "pre-form" of the original apple tree in the seed; just as the organizing energy of animals creates in the sex cells new animals bearing the characteristics of the parent. The organizing power in each case is energy which "works" the sex cell—the plastic "clay" in the construction of new form. The same vibrant energy undoubtedly reaches all the other cells in the organism, but only the sex cells have the property of plastic adaptation. The specific response of a muscle cell is movement; of the visual cell is sight; of a digestive cell is the production of digestive juice; of the thyroid cell is the production of thyroxin; of the sex cell is the production of the new animal or plant. For the creation of the new animal in the sex cell every type of tissue and every organ must contribute its specific part. The cell is as it were a specialized garden in which each of the several organs and tissues through the medium of its specific energy plants its seed. The sex cell during the period of this implantation is passive and plastic; and these specific potential structures lie dormant until fertilization provides energy for the growth and assimilation. The reproductive cell then becomes detached from the energy system of the parent, and the embryonic muscle units, nerve units, liver units, etc., assimilate energy, and then by their own specific energy develop until the entire animal is reproduced. The creator is specific energy; that which is transmitted is specific energy.

In brief, then, our conception may be summarized as follows: As in the adult individual, his personality—his individual characteristics result from specific vibrations in this or that part of his organism in response to environmental influences, the sum total of these electric responses constituting his or her personality; so in the offspring these initial specific vibrations carried through the development of the new individual in external form, in so-called "mental" characteristics, in physiological and in "psychic" tendencies, will determine the personality—the individual characteristics of the new indi-

vidual. And moreover, just as the most facilitated pathways in the adult individual are most influential in establishing the "personality" of the adult, so the strongest characteristics as manifested in the vibrations and electric characteristics of the sex cells will in the main determine the personality of the offspring.

According to this conception, the fertilized ovum would verily be the man in miniature, just as the atom with its central positive nucleus and its negative electrons is a solar system in miniature. In every type of structure from the atom through the most complex chemical compositions to the solar system, this fundamental law of arrangement holds; with infinite variations in arrangement of the positive and negative elements but all holding true to one fundamental principle.

The size and the nature of the atom cannot be directly established. They are determined by reasoning from indirect but tangible evidence. So for the apparently amorphous, fertilized ovum we may reasonably attempt to apply indirect but tangible evidence to determine its organization and potentialities.

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CHAPTER XI

The Uniformity of the Bipolar Pattern from the Atom to Man

It is not expected that either the argument or the evidence which we have presented in support of our conception that man and animals are bipolar mechanisms will prove finally convincing; the only evidence whereby any theory regarding the laws in accordance with which the organism operates can be finally established will be either the successful construction of an organic cell or the ultimate subjection to experimental test of every so-called psychic as well as every obviously physical organic phenomenon. The impossibility of creating a living being on the model of a living being, however, does not invalidate the theory any more than the existence and structure of the atom is invalidated because man cannot construct an atom. In this connection, however, we may point out that whether or not man will ever construct a living being he nevertheless has constructed motor and receptor mechanisms which in manys ways compare in sensitivity to the mechanism of living beings. I refer in particular to the apparatus for the reception and amplification of radio waves, photo-electric cells, etc.

Moreover, we do know the living cell and the atom have a similar physical pattern of structure, and a similar arrangement of their physical forces; and that in each the internal stress as well as the internal balance is similarly staged. Is it then possible to identify a law which governs alike inorganic and organic evolution and points the line of evolution from the atom to man?

An evenly *balanced* atom such as helium, between whose positive nucleus and two negative electrons there is no unbalance, through all time would go on in complete neutrality neither giving nor receiving energy. But a highly *unbalanced*

atom such as hydrogen, with its highly positive nucleus only partially balanced or satisfied by its single negative electron, is vigorously attracted by negative atoms. In the hydrogen atom there is a difference in potential in a bipolar unit of the smallest dimensions. This potential energy—unbalance—and this form of bipolarism is probably identical with the unbalance which is the basic condition of life; but it is not life as we know it; perhaps the principal reason being that this bipolar mechanism, the hydrogen atom, is so far beyond the range of our senses. But if we could place millions of these infinitesimal particles of positive electricity on one side of an exceedingly thin film—4/10,000,000 of a centimeter in thickness—with negative charges on the opposite side, and if we could adaptively charge and discharge these films in work and function, then in the aggregate we would find the hydrogen atom an essential part of a living organism. A single brick is not a building; but millions of bricks with other material may be arranged into many buildings; so a single hydrogen atom is not a living being, but countless numbers of hydrogen atoms with other elements may be arranged into living beings.

It may be supposed that it is the disturbance in the carbon atom caused by the sun's energy that endows the carbon atom with the energy which in combination with hydrogen it carries with it into the cells of animals where it is released in the electric process of oxidation. Thus, energy available for building living beings or for the use of living beings comes from the sun. Chemical action is identical with electric action, for it is the attraction and the repulsion of unbalanced negative and positive elements that makes compounds, solutions, colloids. If there were no atomic, no intermolecular, no interfacial electric phenomena, there would be no compounds, no solutions, no colloids, no life. The atom, the compound, the solution, the colloid, contain as much energy outside as within the living cell, the difference being that in their existence as separate entities the electric energy is balanced and since no difference in potential is established, there is no free energy such as is seen in, and is characteristic of, the living. In addition to the interatomic, intermolecular, interfacial forces, living organisms require free energy between positive and negative poles which

are separated from each other by a sufficient distance so that the current flowing between the poles may by a trigger action release a continuous stream of new energy to perform work. This energy, when governed by the environmental forces, becomes available for the various forms of work and function needed for survival. A bipolar mechanism with films adapted for accumulating an electric charge for its release for the oxidation required to meet the needs of survival is a living thing.

It is not necessary that the negative or cytoplasmic part of the cell should be continuous, or that it should be bound only to one nucleus. For example, Kofoid and others have shown that in certain stages of the life cycle of certain unicellular organisms there may be one continuous cytoplasm with many nuclei of varying size and shape. (Fig. 60.) This is a crucial point in a consideration of the evolution of living matter, for on this basis we can see how a vast amount of the negative colloids in the form of sea-water, mud, soil, might be looked upon as a vast negative mass of cytoplasm; and minute masses of positive colloids, each surrounded by thin films with a high oxidative capacity, might well be considered as positive nuclei.

These positive nuclei we may regard as bacteria. A bacterium might thus be regarded as a first "step-up" from the uniform colloid, occupying together with millions of other like positive nuclei (bacteria) a common cytoplasm—sea-water, soil, mud, etc. If this conception be correct, then we would expect to find that bacteria (nuclei) would stain like the nuclei of cells; and so they do. Since bacteria (nuclei) depend for their existence on a difference in potential between them and their cytoplasm, we would expect to find that bacteria are sensitive to the hydrogen ion concentration of the media; and this is so. For the same reason we would not expect that bacteria could successfully compete for energy—life—with the nuclei of cells; bacteria are rarely found in the nuclei of cells. Bacteria, then, in terms of the bipolar theory, are multiple positive nuclei, occupying in common a continuous negative cytoplasm.

By a fortuitous circumstance, a bacterium might at some moment have acquired for itself some of the cytoplasm or negative colloid which it had shared with other bacteria, and so it would have become independent of the common mass of

HYDROGEN ATOM

CARBON ATOM

MOLECULE of METHANE
(MARSH GAS CH_4)

PHYLUM I PROTOZOA

AMOEBA

FLAGELLATE AMOEBA

GIARDIA MURIS

PHYLUM IX
ANNELIDA

EARTHWORM

PHYLUM X
MOLLUSCA

CLAM

PHYLUM XI
ARTHROPODA

INSECT

FIG. 61.—Schem
the atom t
the blue, th

negative colloids or cytoplasm and would have become the first independent bipolar mechanism, both of whose poles were separated from the common surroundings; that is, it would have become a cell.

Thus, according to our theory, living cells are self-charging condensers, built on the fundamental pattern of the atom, and the molecule, the solution, the colloid and animals in turn are developed into the larger more complicated forms by progressive additions and changes in these bipolar chemical units. (Fig. 61.)

PART III

SUMMARIES OF RESEARCHES

CHAPTER XII

Histological Researches

In the introductory chapter of this thesis have been indicated the successive investigations which led to the development of the bipolar theory. Of primary importance were the histological researches, the findings in which suggested the postulate that the unit cells of the organism are electric cells. For this reason the following brief summary of these studies, which included 2,670 experiments on animals and many observations on man, is offered here.

The Central Nervous System.—The cells of the central nervous system, especially those of the cortex and the cerebellum, were studied in animals which had been subjected to prolonged insomnia, to the injection of toxins, to infection, to the injection of foreign proteins. We studied the brain cells in animals which had been activated in varying degrees from the stage of excitation to that of complete exhaustion by running, by fighting, by rage, by fear, by physical injury, by the injection of strychnin, by the injection of adrenalin. We studied the brains of salmon caught at the mouth of the Columbia River and compared our findings with those in salmon caught at the headwaters. We studied the brain cells of electric fish before and after the partial or complete discharge of their electric organs. We studied the brains of hibernating woodchucks. We studied the brains of humans who had died from hemorrhage, from acidosis, from eclampsia, from cancer, from hyperthyroidism. We studied the brains of animals after excision of the liver and of the adrenals; and after short and long periods of anesthesia with ether and with nitrous oxid. In every instance we found identical histologic changes, chromatolysis and a *loss of differential stainability* of the nucleus and

cytoplasm in the stage of exhaustion, while in animals killed in the stage of excitation, the *differential stainability was increased.*

Of crucial importance in its relation to the inception of the bipolar theory was the finding that in dogs in which the circulation of the head of each dog was anastomosed with the circulation of the body of the other dog (double-crossed circulation) and one dog was subjected to severe abdominal injury, brain cell changes appeared *only in the brain of the injured dog.*

The injection of adrenalin caused immediate increase in the differential stainability of the brain cells followed by a decreased stainability. In double-crossed circulation experiments brain cell changes occurred only in the dog whose brain received the adrenalin; and the characteristic circulatory and respiratory changes *appeared first* (by a minute or more) *in the dog whose brain received the adrenalin.*

After excision of the adrenals and of the liver the differential stainability of the brain cells progressively decreased.

The Liver.—All of the stimuli which produced changes in the brain cells produced constant changes in the cells of the liver. In the stage of exhaustion the cells stained poorly, the cytoplasm was vacuolated, the nuclei were crenated, the cell membranes were irregular, the most marked changes appearing in the cells of the periphery of the lobules.

The Adrenals.—The application of the exhaustion-producing factors listed above in most instances produced destructive changes in the cells of the cortex of the adrenals.

In one group of experiments in which rabbits were subjected to protracted insomnia the cells of every organ and tissue of the body were examined and *histologic changes were found only in the cells of the central nervous system, the liver and the adrenals.*

In a series of experiments in which a protracted period of insomnia was followed by varying periods of rest and sleep we found that brain cells in which the differential stainability was lost and the nuclear membrane was ruptured were not restored. Our findings indicated that the length of time required for the restoration of the cells was in direct relation

to the degree to which the differential stainability was decreased.

Morphin and nitrous oxid anesthesia promoted the restoration of the brain cells to their normal stainability; but the most potent restorative agent was normal sleep.

These histologic studies which indicated that the vitality of the animals studied was in direct relation to the differential stainability of the brain and liver cells, led to a consideration of the essential structure of the cells with the resultant conclusions that variations in stainability indicate variations in the acid-alkali balance between the colloid content of the nucleus and that of the cytoplasm of the cells, hence to variations in potential. Our attention, therefore, was directed to the application of biophysical methods to the study of the function of the cells.

CHAPTER XIII

Electric Conductivity Studies

If we are right in our assumption that the brain is the part of highest potential in the organism—the positive pole—then we would expect to find evidence that the rate of oxidation in the brain is higher than in any other tissue. We would also expect to find that as the result of stimulation the positive and negative poles—the brain and the liver—would respond in opposite directions, thereby increasing the difference in potential between them.

Since an increase in the activity of cells is due in part to an increased permeability of the lipoid semi-permeable films which surround the cells, then if the above assumption is correct we should expect to find that the electric conductivity of the brain is increased and the electric conductivity of the liver is decreased by stimulation. Moreover, since in accordance with the above assumption every alteration in functional activity would be accomplished by variations in the permeability of the cell membranes, then it would follow that every variation in functional activity from whatever cause would be accompanied by alterations in electric conductivity.

In accordance with the bipolar theory, one would expect that during increased activation, such as follows adrenalin injection, the brain would show an immediate increased conductivity, and that in fatigue from excessive adrenalin stimulation, it would show a decreased conductivity; that in the unborn and during the unconscious state of the newborn, the electric conductivity of the cerebrum would be lower than that of the cerebellum and that this relation would be reversed at the time when consciousness appears; that heavy physical trauma which would cause first struggle, then exhaustion, would show first an increase, then a diminution in the conductivity of the brain.

In accordance with the bipolar theory, the state of iodism,

which is the analogue of hyperthyroidism, should be accompanied by an increase in the electric conductivity of the dominant tissues of the body. In accordance with the bipolar theory, excision of the liver and excision of the adrenals should cause a decrease in the electric conductivity of the brain. In accordance with such a theory, one would expect that the injection of acids would decrease conductivity, and that whereas loss of sleep would decrease conductivity, sleep itself would restore the normal conductivity of the brain. The application of these tests was regarded as an essential to prove or disprove the validity of the theory. If a single one of these should fail, the entire theory must fail.

To this end, therefore, a research was undertaken in which measurements were made of tissues from normal adult and immature rabbits, and from fetuses, and from rabbits subjected to various types of exhaustion—insomnia, exertion, fright, infection, surgical shock; to the action of various drugs—stimulant and depressive; to short and prolonged anesthesia, by ether and by nitrous oxid; to the action of adrenalin in single and in repeated doses; to thyroid feeding and to acute iodism induced by the injection of iodoform; to the injection of acids and of alkalies; to the excision of organs—the thyroid, the liver, the adrenals.

The tissues and fluids measured included the cerebrum, the cerebellum, the spinal cord, the liver, the thyroid, voluntary muscle, the heart, the kidneys, the spleen, the lung, the spinal fluid, the blood, the bile.

Our findings in these studies, which included the measurement of the electric conductivity of 4,764 sections from 455 rabbits and 219 sections of pathological human tissues, may be summarized as follows: [1]

1. The specific normal conductivity of the cerebrum, cerebellum and liver can be estimated within a narrow range; while the normal conductivity of other tissues can be estimated

[1] It should be emphasized that in the measurements described here a 1000 cycle alternating current was employed, while in the capacity measurements to be described in a later section, currents of from 800 to 4½ million cycles were used.

within a sufficiently narrow range to determine the order of their relative conductivities.

2. The spinal fluid had the highest conductivity of any of the tissues studied, the lung and the liver the lowest.

3. The order of the conductivities of the following tissues was unchanged in all the animals studied, with the exception noted in (5); viz., spinal fluid, bile, blood, voluntary muscle, cerebrum, cerebellum, liver, lung. In a limited number of observations the conductivity of the heart fell between that of the cerebellum and the liver, but on account of the wide range of the individual measurements, this cannot be considered as established.

4. The conductivity of normal tissues appears to vary according to the season and the general environment.

5. In every normal adult animal studied the conductivity of the cerebrum was higher than the conductivity of the cerebellum. In fetuses and in very young rabbits this relation was reversed—the conductivity of the cerebellum being higher than the conductivity of the cerebrum until about the time when the young rabbit left the nest and began voluntary activities, when the normal adult conductivity relation of the cerebrum and the cerebellum appeared to be established. A most significant corollary to this observation was found in the post-mortem examination of the brains of two patients, one of whom died after days of unconsciousness resulting from a brain tumor, while the other, who died from carcinoma of the stomach, was conscious to the end. In the patient who had been unconscious, *the conductivity of the cerebellum was higher than that of the cerebrum.* In the other patient, as in all our normal animals, the conductivity of the cerebrum was higher than that of the cerebellum.

6. The conductivity of the gray matter of the brain is higher than that of the white matter.

7. Exhaustion from any cause—surgical shock, insomnia, emotion (fright), infection, etc.—is marked by a *diminished conductivity of the brain and an increased conductivity of the liver.*

8. The immediate effect of activation appears to be an increased conductivity of the brain, tending later to decrease as

the stage of exhaustion approaches. This has been shown to be an immediate effect of physical injury; an early effect of the injection of diphtheria toxin; an immediate effect of the injection of adrenalin.

9. Thyroid feeding in large doses over a prolonged period produces the typical symptoms of hyperthyroidism with ultimate exhaustion, accompanied by the changes in the conductivity of the brain, typical of exhaustion from any other cause; i.e., the conductivity of the cerebrum and cerebellum is decreased.

10. Thyroid feeding in moderate doses until the symptoms of hyperthyroidism appear, but not to the stage of exhaustion, produces conductivity changes in the brain typical of the stage of stimulation produced by other agents; i.e., increased conductivity of the brain and decreased conductivity of the liver. These changes were diminished or reversed by the administration of adrenalin.

11. Iodoform increases the conductivity of the brain and the liver. These changes are reversed by adrenalin.

12. The injection of hydrochloric acid produced *diminished conductivity of the cerebellum and cerebrum and increased conductivity of the liver.* The injection of sodium bicarbonate produced *increased conductivity of the cerebellum and cerebrum and decreased conductivity of the liver.*

13. Rabbits were kept awake continuously for 96 hours. At the end of this period a number were killed and conductivity measurements made; others were allowed a brief period of rest of from four days to a week. At the end of the insomnia period the *conductivity of the brain was decreased* and the conductivity of the liver was increased; at the end of the short period of rest, the conductivity of the brain and of the liver was but little changed, if at all; at the end of the longer periods of rest, the brain was again approaching its normal conductivity.

14. A limited number of observations indicate that the changes produced by the injection of a toxin are minimized, provided the toxin is applied in the presence of morphin; that is, excessive doses of a toxin alone decrease the conductivity of the brain and increase the conductivity of the liver; in this limited series of observations the conductivity of the brain re-

mained practically unchanged when diphtheria toxin was administered in a morphinized animal, and the conductivity of the liver was but slightly altered.

15. A limited series of observations of the influence of various agents, which produce marked clinical effects, indicate that the progress of alteration in function produced by any agent is coincident with changes in electric conductivity.

16. In the pathological specimens studied, active malignant growths have a high conductivity in comparison with adjacent normal tissue and the inactive portions of the same growth, and with growths of a non-malignant type.

17. From our findings to date, it would appear that the intracellular changes in exhaustion and shock which are revealed by the microscope are paralleled by alterations in electric conductivity, and that both the histologic and the electric changes bear a direct relation to the vitality of the organ.

CHAPTER XIV

Oxidation—Temperature Measurements

In a bipolar mechanism, variations in functional activity indicate variations in oxidation; variations in oxidation are manifested by variations in heat production. If heat is a constant product of functional activity, then if we could measure the progressive changes in the temperature of the various tissues and organs during the various phases of excitation and exhaustion under conditions identical with those formerly studied, we not only should be able to check our findings in the previous researches, but should be able finally to link those findings with the clinical evidence.

While previous studies had appeared to demonstrate a definite relationship between histologic changes and electric conductivity, this relationship constituting strong evidence in support of the bipolar theory, nevertheless, they did not demonstrate whether or not these apparently related findings were not merely coincident conditions, but corresponded to changes in *function*. Moreover, measurements of electric conductivity must be prosecuted after the death of the animal, although with proper precautions it is reasonable to believe that the changes noted at least parallel the progress of processes in the living animal. To determine finally whether or not the variations in the histologic picture and in the electric conductivity are parts of one and the same process as that manifested by changes in functional activity—oxidation—it was necessary to devise some method by which the rate of oxidation in the cells might be measured in the living animal. Only by such a measure could it be ascertained whether or not changes in electric conductivity indicate changes in oxidation. Clinical evidence would appear to demonstrate that this is the case, but clinical evidence cannot be accurately measured, nor does it identify without question the organs which are princi-

pally concerned. Some accurate index that could be applied to the organ itself in the living animal was essential.

As a means to this end, we decided to use the method of measurement employed by physicists for the measurement of minute variations in temperature, that is, to employ thermocouples so constructed that they could be applied to the brain, liver, muscle or other tissue of the living animal.

These studies have yielded the following results:

1. From the very beginning it was evident that variations in the temperature of the brain under varying conditions parallel variations in the histologic picture and in the electric conductivity of the brain under the same conditions. Thus, the progress of exhaustion from any cause was marked by a progressive decrease in the temperature of the brain and the liver, the rapidity of which was in direct relation to the rate at which the degree of exhaustion advanced.

2. The stage of excitement of ether anesthesia was marked by an increase in the temperature of the brain; but during surgical anesthesia the temperature fell continuously until death. On the other hand, in an animal under nitrous oxid anesthesia, the temperature of the brain remained practically unchanged even during prolonged anesthesia.

3. After hepatectomy the temperature of the brain declined progressively until death, the resultant curve corresponding closely to that produced by continuous ether anesthesia.

4. Muscular activity, either voluntary or produced by direct electric stimulation of a nerve, was accompanied by rapid alterations in the temperature of the brain and the liver corresponding to the phases of the muscular activity—these alterations, however, *being in opposite directions.*

5. *No significant alteration in the temperature of the liver* was produced by the injection of strychnin, of an acid or of an alkali, *although marked and characteristic changes,* corresponding in each case to the clinical phenomena, were produced by each in the temperature of the brain.

6. Exposure of the viscera and abdominal trauma alike produced a rapid fall in the temperature of the brain and the liver, the change in the latter being in part but not entirely accounted for by the direct chilling of the liver substance.

7. The restorative effect of the introduction of hot water into the stomach was marked by an immediate elevation of the temperature of the brain *which measurably preceded—in some instances by a minute or more—the resultant elevation in the temperature of the liver.*

8. Of especial significance were the temperature changes which followed the injection of adrenalin under varying conditions.

(a) In normal animals the temperature of the brain was *increased* by adrenalin, but returned immediately to or below the preceding level.

(b) In normal animals the temperature of the liver was not significantly affected by the injection of adrenalin.

(c) A limited number of observations indicated that the temperature of the spleen, the kidneys, voluntary muscles and intestinal walls was *decreased* by the injection of adrenalin.

(d) *In the absence of the liver the injection of adrenalin produced a diminished or no change in the temperature of the brain.*

(e) In the absence of the thyroid the reaction of the brain to adrenalin was less than in normal animals.

(f) In iodized animals the reaction to adrenalin appeared more promptly and was greater than in normal animals.

(g) After adrenalectomy the reaction to adrenalin was approximately the same as in normal animals.

(h) In morphinized animals adrenalin increased the temperature of the brain but this increase was less than in normal animals and was maintained for prolonged periods.

(i) After the administration of strychnin adrenalin caused an abrupt rise in the temperature of the brain and an abrupt fall in the temperature of the liver.

(j) After hemorrhage the injection of Bayliss' solution diminished the reaction of the brain to adrenalin.

(k) The transfusion of blood after hemorrhage did not affect the normal reaction of the brain to adrenalin.

Of particular significance were the findings, (a) that in voluntary muscular activity and as a result of the direct electric stimulation of a nerve the temperature of the brain and of the liver varied in opposite directions; (b) that upon the introduc-

tion of hot water into the stomach the reaction of the brain in increased temperature preceded that of the liver; (c) that the temperature of the liver was but little altered or was unchanged by the injection of adrenalin; of an acid; of an alkali.

An attempt has been made to establish our assumption that the changes in the temperature of the brain after the injection of adrenalin may be justly ascribed to variations in oxidation. Preliminary experiments have shown that after the injection of adrenalin the temperature of the venous blood coming from the brain was increased to above that of the arterial blood to the brain. This finding if confirmed by later experiments will be a strong indication that the temperature changes within the brain cannot be entirely, if at all, due to variations in the blood supply to the brain.

The findings in these studies which accord with the histologic studies and the electric conductivity measurements support the conclusions, (a) that the brain is the tissue upon which depend the reactions of the organism to stimulation; (b) that the thyroid and the adrenals play essential parts in the production and maintenance of these reactions; (c) that in the performance of its function the brain is indissolubly linked with the liver.

The lack of response of the brain to adrenalin in the absence of the liver, together with the opposite reactions of the brain and the liver, form vital links in the chain of evidence, whereby we may determine the function of each in the bipolar operation of the animal mechanism.

CHAPTER XV

Electric Capacity Measurements—Thickness of Cell Membrane

The organic cell may be compared to a condenser of the type of the Leyden jar in which the charge is accumulated at the surface of a dielectric between two conductors. In the case of the cell the two conductors are the electrolytic fluids within and without the cell; the dielectric is the comparatively non-conducting lipoid membrane. In a condenser of this type the thinner the dielectric the higher is the capacity. The capacity of such a condenser may be computed from the formula $C = \frac{SK}{4\pi a}$, in which S is the area of the surface in sq. cm. of the dielectric, K is the dielectric constant and a is the distance in cm. between the surfaces of the dielectric. It follows that the greater the area of the surface, the higher the dielectric constant, and the thinner the dielectric, the greater will be the capacity of the condenser.

In referring the elements of this formula to the biologic cell we find that the cell membrane is lipoid in character and has a dielectric constant of the order of 3.

By experimental methods Dr. Fricke has established for the red corpuscles a capacity of 0.8 microfarads per sq. cm. of cell surface; and, reversing the above formula, has calculated from this value the thickness of the cell membrane, finding it to be of the order of 4/10,000,000 of a centimeter in thickness—i.e., of the thickness of a single molecule of oil.

In a previous section we have calculated that assuming an average diameter of 30 microns, the estimated approximate number of nerve cells—3,000,000,000—would give a total surface area of 8.48 sq. meters (91.4 sq. feet); for the estimated number of nerve cells of the cerebral cortex—1,200,000,000—

the total surface area would be 3.36 sq. meters (36.4 sq. feet); and for the estimated number of large cells in the cerebellar cortex—10,000,000—with an average diameter of 100 microns, the total surface area would be 0.32 sq. meters (3.4 sq. feet). On the basis of Dr. Fricke's capacity value per sq. cm. the total capacity values of these areas can readily be calculated. Thus, for the cerebral cortex alone the total value would be 26,880 microfarads. The significance of this capacity value is shown by the fact that this would be the capacity value of a Leyden jar made of glass one-third of a millimeter in thickness with a total surface area of 114,000 square meters (2.8 acres).

Such a Leyden jar with a capacity equivalent to a single cell with a diameter of 30 microns would have a surface of 0.95 sq. cm., while a Leyden jar with a capacity equivalent to that of the large brain cells with a diameter of 100 microns would require a surface of 10.2 sq. cm.

While these comparisons are interesting, they are not so significant as those which give the amount of heat which would be required to supply such a difference in potential as is indicated by existing evidence. To establish a difference of potential of one volt across one farad requires 0.12 gram calories. To establish the potential indicated by the value of 0.8 microfarads per sq. cm. of cell membrane, for the total surface of the 1,200,000,000 cells in the cerebral cortex would require 3×10^{-3} gram calories.

The figures given above not only express the high capacity value of the brain cells, but they show also that the energy which is fabricated in the brain is measurable in electrochemical units.

PART IV

SUMMARIES OF CERTAIN GENERALLY ACCEPTED FACTS IN THEIR RELATION TO A BIPOLAR ORGANISM

CHAPTER XVI

Certain Established Facts Regarding Electric Energy and its Relation to Other Types of Energy Concerned in the Operation of the Organism

The energy of animals is derived from the sun, in small part directly, in large part from the light energy stored in plants in the form of carbohydrates. But just as the plant cells cannot transform simple elements into carbohydrates without light, and as many chemical processes require for their initiation a radio-active, thermal, electrical or other catalytic agent, it is assumed that a catalytic agent is required to excite the activity of the cells of the body, whether that activity is to be expressed in terms of thermal, chemical, mechanical or electrical energy. What form of energy constitutes this catalyzing agency? As stated in Chapter II, the existing forms of energy among which the choice must lie are heat, light, gravitation, intermolecular forces (surface tension, adsorption), chemical energy, electric energy. It is obvious that neither heat energy nor any mechanical force can be transmitted by the nerve fibers to act as a catalyzing agent upon the various types of cells in the organism, exciting in each the type of activity demanded for the performance of its specific function. The form of energy to be identified, therefore, must be intermolecular or chemical or electric energy.

Since electricity controls chemical and intermolecular action, and since chemical action—oxidation—controls the production of electricity in an electric cell constructed after the pattern of the cells of the organism, we conceive that electricity liberated in the cells of the central nervous system by oxidation and conveyed to the cells by the nerve fibers acts as a catalyzing agent by means of which the energy in each cell of the organism is

controlled by nerve action. In cells which are not innervated, the same structural arrangement is found; and in these cells also oxidation is the source of energy.

Electric Energy

To enumerate the facts reported by many investigators regarding the rôle of electricity in vital processes would require a large volume in itself and would not be pertinent to the purposes of this thesis. We shall therefore confine ourselves to an enumeration of only those generally accepted facts regarding electricity which are especially pertinent to our conception of man and animals as bipolar mechanisms.

Electricity is omnipresent in all forms of matter, in atoms, molecules, solutions, colloids. Electricity passes by means of conductors from a point of higher potential to one of lower potential, always along the path of least resistance. At any point in its passage the electric current is capable of transformation into heat energy, mechanical energy or chemical energy. An electric current is produced by a generator or battery whereby a difference of potential is maintained between the poles.

Two colloidal solutions of different H-ion concentrations separated from each other by a semi-permeable dielectric partition constitute an electric cell, within which the potential difference bears a direct relation to the difference between the H-ion concentrations of the two solutions.

The difference of potential created by a cell or battery will pass along conductors to points of lower potential. If there are gaps—synapses—in the conducting paths a sufficient difference of potential between the two ends of the path makes it possible for the electric current to bridge this gap.

Histologic studies by Dr. M. L. Menten and Dr. J. B. Austin have shown that the physical structure of the brain cells of electric fish is changed after the electric organ is discharged. (Fig. 62.) Dahlgren [1] has found that the electric organ of the electric fish does not store electricity but that it is capable of the instantaneous production of electricity by means of oxidation and that this process of oxidation within the electric organ

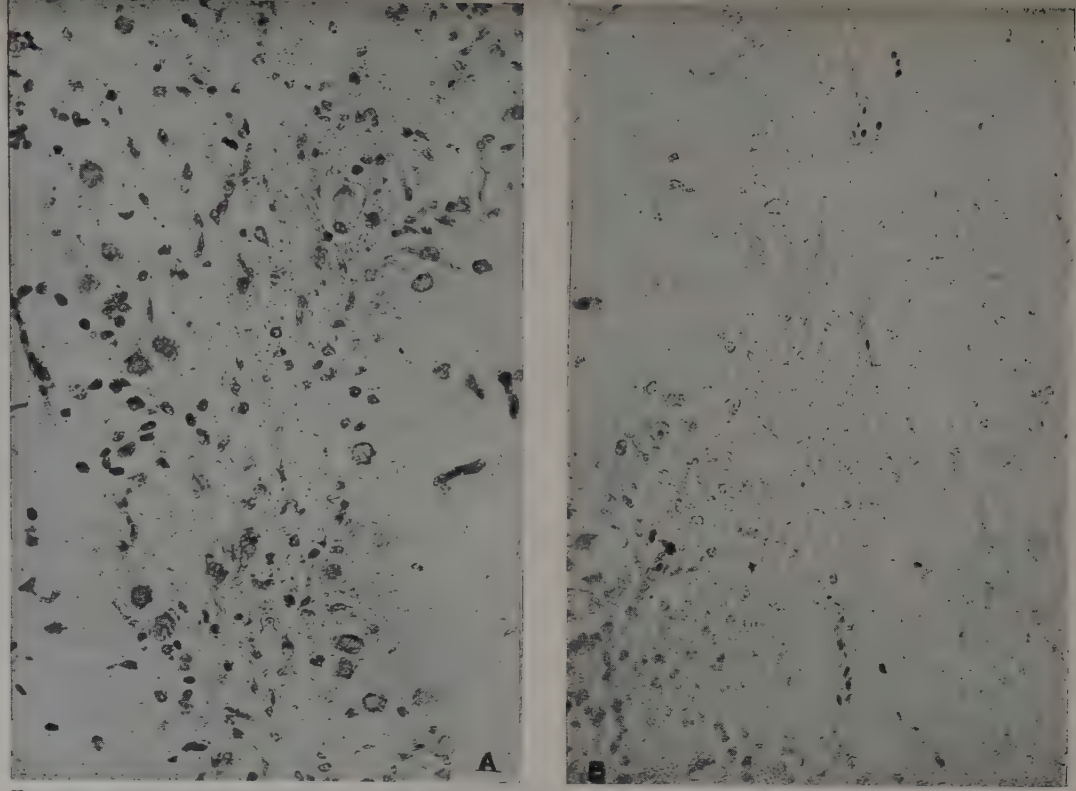

FIG. 62.—Effect of the discharge of its electric organ on the brain cells of a torpedo. A. Section of cerebro-electric lobe before discharge. B. Section of cerebro-electric lobe after discharge. (From photomicrographs × 310.)

is not performed if it is disconnected from the brain. This last observation, as stated in Chapter III, was made by Galvani in experiments described by Becquerel.[2]

Finally, of the utmost value in its support of the conception that the organism as a whole is operated by electricity should be cited the biological fact that the application of electricity to organs or tissues can make them perform all the functions which they normally perform under nervous stimulation.

Light Energy

Although the relation of light energy to the electric energy which operates the bipolar animal organism may not at first be apparent, the following facts are peculiarly significant: (1) that there is increasing evidence that the original unit of living matter was organized from the inorganic elements of the sea by means of electric energy or sunlight; (2) that living organisms, even those whose lives are spent in apparent darkness, live in a world the atmosphere of which is constantly subjected to a bombardment of electrons from the sun; (3) that the energy of heat and light is essential for the production of chemical action; and (4) that the energy transmitted through one of the most delicate and intricate mechanisms in man as the result of the impact of light waves, has been demonstrated to be electric energy. It is therefore fitting that we consider briefly the physical qualities of light and its biological effects in their relation to a bipolar mechanism.

According to the electronic theory "light waves" are electric waves, and the light of the sun is electric energy transmitted by the constant emission of electrons from the vast number of electrons constantly vibrating within the body of the sun itself. Light, then, is electricity, and the effects of light are the result of the application of its electrical energy and are to be interpreted by the laws which govern electrical energy.

That sunlight is electricity is shown by its capacity to induce positive charges. This has been demonstrated by Nodon [3] in his observations of the electric action of the sun and moon, from which he concludes that "the sun induces a positive elec-

tric charge" and that "the full moon produces a positive electric induction analogous to that of the sun."

Various investigators have produced formaldehyde by the action of sunlight on water and carbonic acid in the presence of salts of iron or other inorganic salts; and by the further action of sunlight or of ultraviolet light on formaldehyde, carbohydrates—sugars—have been produced. That is, sunlight—electric energy—can produce organic compounds from inorganic elements.

The phenomena of heliotropism as demonstrated by Loeb and his conclusions therefrom are strong arguments in favor of the assumption that the animals thus activated are electric mechanisms and that the energy that activates them is electricity.

Heat Energy

The facts that there is an optimum and a lethal temperature for every type of life; that variations in one of the most fundamental processes of life—oxidation—are accompanied by variations in temperature, make it essential to consider a few of the more important physical properties and biological effects of heat in their relation to electric energy.

Heat in common with electricity and with light is radiant energy, but while the latter forms of energy are electronic phenomena, heat is concerned with the activities of atoms and molecules. As heat is radiant energy, its manifestations are governed by the same primary physical laws as those which govern electric energy and light energy. Moreover, in its manifestations in living organisms and in inorganic matter, heat energy is indissolubly linked with electric energy, light energy and chemical energy.

Of primary importance is the fact that "were there no heat or light, or were the intensity of these below a certain limit, depending on the nature of the substances, we could get no chemical action. Thus inertness would probably be a property of *all* substances in the dark at the so-called absolute zero of temperature." (Comstock and Troland.)[4]

Conversely, heat promotes chemical action. When we con-

sider that chemical action means an alteration of atomic relations, and hence of electronic relations and that the relation between heat and oxidation is reciprocal, that heat promotes oxidation, oxidation producing heat, the direct relation of heat to the electric phenomena of the organism becomes apparent.

An equation has been established by means of which the heat of ionization of water may be related to the ionization constant of water, and this equation is equally

"applicable to the ionization process of electrolytes in water. If the ionization values are known at different temperatures, the energy change accompanying the ionization process may be calculated, assuming that the energy change accompanying the process remains constant. . . . It appears, thus, that a knowledge of the thermal properties of electrolytic solutions has a very direct bearing on our interpretation of the phenomena observed in electrolytic solutions. . . . In this connection, it should be noted that a number of investigators, from a study of the temperature coefficient of the electromotive force of concentration cells have obtained values for the energy changes accompanying the transfer of electrolytes from solutions of one concentration to another." (Kraus.) [5]

Whether or not this equation and its derivatives can be practically applied to the biologic concentration cell, these observations throw still further light upon the electro-chemical rôle of heat in the organism:

"The extraordinarily good heat conductivity of metals is accounted for in terms of the free electrons which they contain. If this is the true explanation, it can be shown to follow that, other things equal, those metals which contain the largest number of free electrons will be the best heat conductors. But such metals will also be the best conductors of electricity, and hence it would appear that some sort of proportionality should exist between the power of a substance to conduct heat and its power to conduct electricity. Accurate measurements and calculations show that a relationship of this kind holds in nature, and that its quantitative character is in remarkable accord with the assumptions of the electronic and molecular theories." (Comstock and Troland.)[6]

This is strongly in accord with the electro-chemical conception, for our researches have shown that the electric conductivity

of tissues bears a direct relation to their chemical activity, hence rate of oxidation, hence ionic activity, hence free electrons.

That heat is favorable to the growth of plants while cold retards growth, is a common observation; that there is a definite limited range of temperature within which each type of living organism can exist is well known; that all the major activities of life are accompanied by variations in the manifestation of heat is a universal experience. That the chemical reactions which accompany the operation of the mechanism must be accompanied by variations in heat production is the direct corollary of the physico-chemical facts.

The source of heat within the organism has always been the subject of discussion, Lavoisier being the first to prove that it is the result of the combustion of the tissues themselves. Following Lavoisier various investigators have endeavored to locate the principal site of this combustion in some specific organ or tissue—the lungs, the blood, the muscles, etc. It is only within comparatively recent years that it has been generally accepted that the combustion takes place within the living cells themselves.

Interatomic, Intermolecular and Intramolecular Forces

When atoms, according to the positive or negative preponderance of the charges of which they are composed, are grouped into molecules, the resultant electrical charges of the molecules in turn are positive or negative. The manifestations of these molecular charges produce those types of energy which are designated intermolecular or intramolecular forces. These forces are variously manifested in gases, solids and liquids. In the phenomena of living organisms we are principally concerned with the intermolecular forces of solutions which are manifested as surface tension and osmotic pressure. The phenomena of sound and of heat are the result of molecular activity. In the final analysis, however, as has been stated in our discussion of the different forms of energy, all of these phenomena are due to electrical forces.

Nernst's application of the osmotic theory to the mechanism of current-production in solutions is of especial interest in this discussion and is given at length in the Appendix, as is Loeb's description of the relation of the intramolecular forces in biological cells to electrical phenomena.

In view of all these facts, which demonstrate the omnipresence of electricity in vital phenomena, its versatility, its relation to thermal, light, chemical and intermolecular energy, its production by oxidation, its identity with sunlight—all these characteristics present overwhelming evidence that electricity is the energy by means of which living organisms operate. In addition, the fact that electrical currents operate in a circuit between points of highest and lowest potential is in accord with our conception that such a circuit exists in all living organisms from the unicellular protozoan to man.

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CHAPTER XVII

The Electrical Significance of Certain Established Facts Regarding the Principal Constituents of the Animal Organism

Among the important constituents of living matter are hydrogen, oxygen, nitrogen and carbon in combination in water, carbohydrates, proteins and lipins; and certain inorganic salts, especially those of potassium, sodium, magnesium, calcium, iron, sulphur, chlorin and phosphorus. Each of these contributes its share to the complexity of reactions which constitute living processes, but we shall consider here only those elements or compounds the presence of which is primarily essential to the electrical operation of the organism—water, oxygen, hydrogen, potassium and other electrolytes, oils and carbon.

Water

Water constitutes from 70 to 90 per cent of the body weight. Water is therefore the vehicle in which the organism is suspended. Among the various properties of water which render it of value to the organism, there is one which has an essential and vital relationship to a consideration of the organism as a bipolar mechanism: water has an extremely high dielectric constant which means that it has a very high ionizing power as a solvent. Its ionizing power is so high that absolutely pure water is unobtainable, the purest which can be obtained always containing hydrogen and hydroxyl ions in solution. Moreover, water is not, as commonly considered, a simple inert substance, but is complex and unstable in its constitution. The structure of the water molecule is not constant, but is influenced primarily by temperature, and by the substances which it holds

in solution. These variations in molecular structure in turn influence its ionizing power; and variations in ionizing power mean variations in electrical properties.

By virtue of its catalyzing power water promotes chemical action, which in turn promotes the production of energy.

Water facilitates oxidation. "It is only in the presence of water that oxygen has the power of oxidizing rapidly." (Mathews.)[1] Therefore, before oxygen can become available for use in the cell it must be dissolved in water.

Water has a high specific heat. Since an elevation of temperature of one degree centigrade increases chemical activity 10 per cent and electric conductivity 2.5 per cent, it is essential that the bipolar units of the organism be protected against such extraordinary activations or depressions as would result from comparatively slight variations in temperature. This need is met by the fact that each cell is practically suspended in a medium of a high specific heat.

One other property of water has a fundamental bearing on the bipolar character of the cells, namely, the immiscibility of oil and water. This property makes possible the establishment of the semi-permeable lipoid cell membranes. These lipoid films which separate the cells of the body from each other and from the surrounding fluids; which separate the nucleus from the cytoplasm; which separate the spherules (Mott) within the cells from each other and from the other parts of the cell—these films could not have been established in a medium of an oil or lipoid solvent but only in a water medium.

Electrolytic Solutions and Colloids

Electrolytes in solution, especially aqueous solution, conduct the current. According to the electrolytic theory this is explained by their dissociation into ions. Salts as a rule dissociate readily, acids and bases dissociate in varying degrees.

When to this statement we add the facts that the protoplasmic contents of the cells consist of water, oils and salts; that in some instances 94 per cent of living matter consists of nothing more unusual or remarkable than water and the com-

monest salts; and that water will hydrolyze any salt until the product of the hydroxyl and hydrogen ions reaches a value of about 10^{-14} (Bancroft) [2], thus setting free the metal ions, each with its definite electrical charge, the vital importance of these electrolytes to the electric activity of the cell is at once apparent.

Of especial value in relation to the bipolar theory is the influence of electrolytes upon the type of emulsion in which they are dissolved. Studies by Clowes, by Loeb, and by Osterhout are of especial significance in this direction.

"These salts are not mere inert substances, they are not simply absorbed with the water and tolerated, but they are in combination, in part at least, with the organic matter of the protoplasm. They are not simply clinkers clogging the grates of the protoplasmic fires, but they are active in the production of the vital phenomena. Indeed, some have gone so far as to believe, as we shall see, that by means of the electrical charges they bear when in solution they vitalize the colloidal, organic substratum of the cell and make it alive. Any change in their relative proportions at once affects the activity of the cell; thus by increasing or decreasing the proportion of sodium, calcium, or potassium, skeletal muscle may be made to twitch rhythmically or to remain at rest; nerve impulses may be set up in motor nerves, or the irritability of the nerve raised or lowered; chromophores of fish scales may be contracted or expanded; and the activities of all cells increased or diminished. . . . Furthermore, by increasing the total amount of salt in protoplasm many cells may be stimulated and egg cells of some animals caused to develop parthenogenetically without the aid of sperm." (Mathews.) [3]

"This antagonistic action of sodium and calcium salts with reference to emulsions throws light upon some perplexing physiological problems. Jaques Loeb showed that certain marine organisms died in sodium chlorid or calcium chlorid solutions which were isotonic with sea-water; but flourished when there was a definite ratio of sodium to calcium, a result which could not be explained on the basis of osmotic pressure. If we consider protoplasm as consisting of lipoids (oils) and water, we shall have an emulsion of oil in water in presence of calcium salts. When the sodium and calcium salts are present in a definite ratio, there will be a balancing between these two types of emulsion, and it may well be

that this critical state is the one which is conducive to life and growth. As a matter of fact, Clowes found that the ratio of sodium and calcium salts necessary to produce a balancing between the two types of emulsions when working with oil, water and soap, was practically the same as that found in sea-water. This indicates a very close connection between the two sets of phenomena. Osterhout of Harvard has shown that the specific electric conductivity of certain seaweeds is increased by addition of sodium salts and decreased by the addition of calcium salts. If the hypothetical emulsion changed to one of oil in water, the conductivity should increase, and it should decrease if the emulsion changed to one of water in oil." (Bancroft.)[4]

Although the validity of Clowes' application of his discovery of the reversal of phases in oil emulsions by electrolytes to changes in protoplasmic permeability is questioned (Seifriz),[5] there can be no question that variations in the ionic concentration of the elements within the cell must play an indispensable rôle in the production of the activities of the cell as an electrical unit.

Oxygen and Hydrogen

Oxygen, the "acid maker," is essential to the life of the cells. Oxidation produces acids. Is the production of acids the essential rôle of oxidation?

If a state of suboxidation of the cells is induced by protracted hemorrhage; by any interference with the intake of oxygen as by gradual asphyxia from any cause; by interference with the absorption of oxygen in the alveoli of the lungs as in pneumonia; or by loss of the oxygen-carrying property of hemoglobin as in carbon monoxid poisoning—whatever the cause of the suboxidation, the differential stainability of the cells is diminished or lost, the diminished energy-transforming function being manifested in the organism as a whole by a diminution of mental and physical energy which is progressive until equilibrium of the acid-alkali balance—death—is established.

These facts indicate that the acids produced by oxidation in turn produce the essential alterations in the difference of poten-

tial between the nucleus and the cell-body and probably between parts within the cytoplasm (Mott), as a result of which accumulations of acid and an adaptive discharge of energy are provided. Water carries the oxygen in solution to the cells, dissolves the acid by-products of oxidation, and bears them away from the cells, thus constantly restoring the acid-alkali balance which is as constantly altered by the acidulating oxygen. It would appear, therefore, that water and oxygen in a vital and inseparable relationship are essential to the production of the electrical variations within the cells, the manifestations of which, as it would appear, constitute life.

Reduction is as vital a function of the cell as is oxidation. The most active oxidizing agent, as one would suppose, is oxygen; the most active reducing agent is hydrogen. By means of oxidation the strongly positive hydrogen ion is released; by means of reduction it is bound, and therefore by the constant interplay of the oxidizing and reducing activities within the cell its electric potential is varied with consequent variations of the phenomena of the cell. "As a reservoir of life energy which is liberated by oxidation, hydrogen exceeds any other element in the heat it yields, namely, 34.5 calories per gram, while carbon yields 8.1 calories per gram." (Osborn.)[6] It would appear, therefore, that the rôles of hydrogen and of oxygen in the activities of the cells are interdependent.

The hydrogen atom is the smallest and most swiftly moving atom, and also the simplest and the most unstable in its construction. It consists of a positive nucleus around which revolves a single negative particle of electricity. Its instability as compared with an atom of helium, the nucleus of which is bound with two electrons, is obvious. By reason of this symmetrically balanced structure the atom of helium is comparatively inert; the unbalanced hydrogen atom is readily disrupted. Because of its instability the hydrogen constituent is readily released from compounds by oxidation and is itself disrupted, setting free the positive nucleus of its atom—the hydrogen ion, the negative electron in combination with oxygen forming the hydroxyl ion.

The Interrelationship of Hydrogen Ions and Hydroxyl Ions

Throughout life the relation between the concentration of hydrogen ions and of hydroxyl ions is maintained within certain narrow limits of variation. It would appear, therefore, that these ever-present ions and the relation between them are essential to the operation of the bipolar mechanism.

Water is an electrolyte and dissociates into H- and OH-ions, the H-ions being positive, the OH-ions negative.

Hydrogen and hydroxyl ions have the highest ionic conductance. Therefore, "the addition of water to a solution of a weak acid greatly increases the conductance of that acid."

If, as Kraus states,[7] in aqueous solutions the hydrogen atoms combine with oxygen, the resultant OH_3 ion would be still more strongly positive. By means of oxidation on the lipoid films electric energy would be released, as a result of which the swiftly moving H-ions would pass through the semi-permeable lipoid membrane, but would be held there by the negative ions accumulated on the inner surface. Thus, on one side of the dielectric membrane would be accumulated the positive charges of the $H - OH_3$ ions, and on the inner surface the negative charges of the hydroxyl ions, thus establishing at the membrane a difference of potential. This would be true of all cells in the body. But since the speed of production of H-ions is in direct relation to the rate of oxidation, the accumulation of H-ions in the cells of any tissue and hence the electric potential of that tissue would depend upon its oxidative power. Certain portions of Loeb's "Theory of Colloidal Behavior" are of especial significance in this connection. (See Appendix A.)

Oils and Fats

We have already suggested the interrelation of oil and water in a bipolar mechanism and have discussed in part the function of the lipoid films of the cells in the accumulation of electric charges. It is important, however, to include a brief further

statement regarding the characteristics of oils and of lipoid films which make them essential to the electro-chemical operation of the organism.

Many oils absorb oxygen; thus the oils used in paint, for example, do not dry by evaporation but by oxidation. The oxidation of fats produces more energy than the oxidation of the sugars from which they are derived. "The system oxygen-fatty acid contains, therefore, far more potential energy than the system oxygen-carbohydrate. One gram of fat burned produces nine calories of heat as compared with four for a gram of carbohydrate." (Mathews.)[8]

There is a reversible relationship between fats and carbohydrates. Thus by the action of an enzyme, possibly lipase, the reaction by which a carbohydrate is converted into a fat may be reversed. This reversible action in plants has been extensively studied by Ivanow. (See Appendix A.) The reversible phases of sugar and fat metabolism may give a clue to the sequence of the oxidation processes in the cell.

As already stated, the fact that neutral oils and fats are insoluble in water is of prime importance to the conception that the cells are bipolar units, since upon this relationship of water and oil depends the establishment of the lipoid membranes of the cells. It should be added that among the substances in which oils and fats are soluble are ether and chloroform, a fact which has an important physiological and clinical significance.

Lipoid Films

The finding by Dr. Fricke in our laboratory that the lipoid cell membranes are of the order of four-ten millionths of a centimeter in thickness, added to the fact that oils have a high dielectric constant, is of the highest electro-chemical significance, since the thinner the film the higher its electric capacity.

The importance of the semi-permeable lipoid membranes of the cells for the establishment of an electric potential has been indicated by the Donnan theory of membrane equilibria, and by the researches of Beutner,[9] Loeb[10] and others on the phenomena of colloidal behavior. Loeb's discussion of the

"origin of the electrical charges of living cells and tissues" is of especial importance in this connection. (See Appendix A.)

Potassium

Among the characteristics of potassium which appear to be of prime significance in their relation to the essential rôle of potassium in the bipolar mechanism, the following are especially significant.

Potassium is omnipresent in living organisms except in the nuclei of the cells. It is the only radio-active element in the body. It has the power of orientating and maintaining the orientation of other ions. It is "an absolutely necessary constituent of the fluid used for the perfusion of an organ. If a potassium-free Ringer's fluid is passed through a frog's heart the heart will come to a standstill in about half an hour." "No non-radio-active element has been found which is capable of acting as a substitute for potassium." "On account of its unit negative charge, it has a disturbing effect on all systems in electrical equilibrium through which it passes." (Burns.) [11]

Mathews suggests that potassium is concerned in the respiration of cells.

"Another substance which is in some way concerned in the respiration of cells is the element potassium. It has been found that in the presence of potassium hydrate, phloroglucin and similar substances undergo oxidation better than with an equivalent amount of sodium hydrate. This indicates that the potassium salt is more easily oxidised than the sodium. There must be some reason for the preference cells have for potassium over sodium. The general richness of potassium in cells of widely different character indicates that this element must be concerned with some fundamental process or condition in the cell, and it is possible that that process is respiration. But just why it is favorable or what its real function is it is impossible to state." [12]

Carbon

Among the normal constituents of living matter, one other, carbon, deserves especial consideration because of certain prop-

erties which render it of essential value to the bipolar function of the cells.

Nernst [13] states that "it is doubtless carbon itself which stamps its character on the 'chemistry of the carbon compounds,' " and offers the following arguments brought forward by van't Hoff in partial explanation of the preëminent position of this element in organic compounds:

"1. The quadrivalence of carbon necessitates an enormous number of derivatives of a carbon compound.

"2. The capacity of carbon atoms of uniting with each other in very many ways, allows the possibility of the greatest variety of combination.

"3. The position of carbon, standing as it does between positive and negative elements, invests it with a peculiar capacity for uniting with the most different elements, as hydrogen, nitrogen, oxygen, chlorin, etc. To this is due the property of adapting itself alternately to the processes of oxidation and reduction, which have such significance in animal and plant life."

It has been estimated that "about two hundred thousand distinct compounds of the element carbon are now known, most of which are with only three other elements: hydrogen, oxygen and nitrogen." (Comstock and Troland.) [14] Moreover, the isomeric property of carbon compounds vastly extends the occurrence of this element in organic matter. "The organic chemist is acquainted with twenty-six different compounds which contain four atoms of carbon, six of hydrogen and three of oxygen, and with one hundred and fifty-seven which are composed of ten atoms of carbon and sixteen of hydrogen." (Comstock and Troland.)

Mathews suggests that since every battery must contain a conductor of the first class that essential is provided by the chains of carbon molecules:— "A stick of highly compressed graphite is a good conductor, and the chains of carbon atoms are nothing less than very minute and highly compressed rods of graphite. We may then conclude that certainly molecules made of carbon atoms must be good conductors. . . .

"The fact that protoplasm is composed so largely of molecules consisting of chains of carbon atoms which are hence con-

ductors of the first class is a matter of great importance in understanding the electrical phenomena, catalysis, and synthesis of cells." [15]

The importance in a bipolar mechanism of an element with these characteristics is evident, especially when we take into consideration the fact that carbon shows the highest tendency to unite with oxygen. This high oxidizability together with the manifold combinations of carbon makes possible the continuance and variety of degrees of oxidation in the various types of tissues in the body, whereby in each the difference of potential specific for that tissue is maintained. "Thus Barrell observes that a chemist would immediately put his finger on the element carbon as that which is needed to endow an organic substance with complexity of form and function, and its selection in the origin of plant life was by no means fortuitous." (Osborn.) [16]

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PART V

CONCLUSION

CHAPTER XVIII

General Conclusions and Summary

The purpose of this thesis has been to present certain evidence and discussions based upon that evidence in support of the theory that man and animals are bipolar mechanisms and that the organism not only is driven by electricity but that it was originally created and constructed by electrical forces.

Our thesis is based upon the fundamental conception that life is a dynamic not a static phenomenon, and that, therefore, to attempt to define living processes in terms of their histological structure is as inadequate as to attempt to interpret the phenomena of the solar system in terms of the elements of which the sun and the planets are composed. The phenomena of the solar system are dynamic phenomena. The physicist has discovered that the phenomena of the molecule, of the atom and of the electron are dynamic phenomena, so, also, must the phenomena of living beings be interpreted. They are dynamic phenomena and can be interpreted, therefore, only in terms of that type of energy whereby they are produced. Any consideration of the structure of living organisms therefore must be related to the manner in which that structure is utilized in the dynamics of the organism as a whole.

Certain characteristics, therefore, which pertain to all living organisms should be summarized here since upon them the development of the bipolar theory primarily depends.

1. The organs, the cells, the functioning parts within the cells are interrelated by means of nerve fibers and protoplasmic bridges forming a syncytium (Sedgwick). The energy units of the protoplasm itself are interrelated by means of a meshwork of protoplasmic threads. Living matter, therefore, is structurally equipped for a *universal circulation of energy.*

2. As universally present in living matter as the intercommunicating fibers. or lines of force, are the lipoid films. These

films separate the cells from each other; they separate the electrolytic solution within the cells from the electrolytic solution in which the cells are suspended; they separate the nucleus from the cytoplasm and from the nucleolus. Lipoid films also bound the spherules and granules within the cell. They are universally present in protoplasm.

3. In living organisms an acid-alkali balance on opposite sides of the dielectric films is maintained by a difference in the concentration of H- and OH-ions.

4. Living tissues have electric capacity.

5. Living tissues contain certain electrolytes among which potassium is of primary significance since it is radio-active and has the power even in combination of orientating other molecules at a distance.

6. Electric phenomena are always present in living matter.

7. The living transformer of energy obeys the same laws of the conservation of energy as do non-living energy transformers.

8. Irritability, assimilation, reproduction, the universal characteristics of living matter as distinguished from the non-living, are electric phenomena.

9. The structure of the molecules and atoms of living systems is that of a crystal. In the non-living crystal the lines of force are static and the crystal grows by accretion. In the living crystal the lines of force are dynamic and the crystal grows by reproduction.

On the foundation of these universal characteristics of living matter has been constructed the bipolar theory, the argument in favor of which may be briefly summarized as follows:

The living and the non-living are chemically identical, the living differing from the non-living not in substance but in the utilization of non-living material for the construction of mechanical devices that have the power of transforming energy and of reproducing themselves.

In accordance with the bipolar theory, these processes which distinguish the living from the non-living are due to electrical forces within the protoplasm, which endow the protoplasm with the essential qualities of irritation, assimilation and reproduction. It is due to these electrical processes that groups of the

protoplasmic energy units become associated in cells. Within the cells identical electrical forces produce the mitotic processes by means of which are formed the paired identical parts, each of which forms a new cell. And even before the protoplasm is formed, electric forces arrange the atoms and molecules as building stones, each in its own place, to form the essential structures of the protoplasm.

Moreover, not only do electric forces construct the component structures of the cell but they arrange the atoms and molecules of the structures outside the cell which play their part also in rendering effective the electric charges created within the cell itself.

In accordance with the bipolar theory, we believe that the potential within the cells is created by variations in oxidation on the two sides of the condenser plates—films—which separate the nucleus of the cell from the cytoplasm and the cytoplasm from the surrounding medium. Thus, in each of the trillions of cells of the body there is created an electric strain, the vibratory discharges of which serve as the catalyst which produces oxidation, oxidation in turn renewing the electric charges on these countless interfaces within the cells.

With the diminution of the difference in potential, with the lessening of the frequency and force of the vibratory discharges, there develops successively diminished vitality, fatigue, exhaustion, unconsciousness, until equilibrium—death—ends the sequence. Or the frequency and intensity of the vibratory discharges may be temporarily suspended by inhalation anesthesia or by sleep, the difference between these processes, however, being that in the former the difference of potential upon which the degree of electric strain—the force of vibratory discharge—depends is being progressively diminished, while during the latter—sleep—the potential which has been lessened during periods of consciousness is being built up—restored.

Thus the specific characteristic which differentiates the living animal organism from the non-living materials of which it is composed would appear to be the frequency and force of these electric discharges rather than its static structure. An animal, therefore, is an energy phenomenon rather than a form phenomenon.

On the basis of this assumption, it is necessary to identify the original source of the forces which transmitted this characteristic to the atoms and molecules of the colloids within which the first living organism arose. This we may assume to have been the vibrant energy of light which obviously is the ultimate source of life. We thus assume that life may be defined as the expression of the specific energies emitted by atoms and molecules, which energies in turn were given them by light. In accordance with this conception the composition of the living organism must be constantly changing. Electric energy governs the composition of the structure of the organism and the composition and arrangement of the structure in turn makes possible the transformation of energy. That is, the energy and structure of the organism is constantly changing and yet apparently the structure and the energy remain constantly unchanged.

An analogy to this cycle of static and kinetic changes within the organism is offered by the rainbow which appears to be static and stationary although rays of light are swiftly passing through the swiftly falling drops of water. The rainbow seems to be static because the effect of each wave of light on each drop of water is the same as that of its predecessor. In other words, the rainbow is the result of an infinite series of equal variations in electric strain among an infinite number of atoms and molecules, the arrangement of which is stationary and characteristic although the atoms and molecules which constitute that arrangement are constantly changing.

We may imagine that by the electric forces of light a positive charge was transmitted to infinitely small particles of matter of ultramicroscopic size, thus producing a difference of potential between these particles and the negative electrolytic solutions in the sea or in the mud which surrounded them. When this difference of potential reached a certain point we may conceive that a discharge took place with an immediate rebuilding of the differences of potential; this process continuing until these small particles of matter built up a permanent mechanism for the maintenance and interchange of electric forces—thus creating the first mass of protoplasm. This small mass of protoplasm by its greater power of oxidation would

have been positive as compared with the negative electrolytic solutions by which it was surrounded, and therefore by a like process of discharge and immediate rebuilding of potential would have finally permanently acquired an electronegative portion which became the cytoplasm of the first cell.

By the continuance of these alternating processes created by an alternation of electric strains and discharges, we may suppose the primary cell or cells grew and became increasingly complex until by some fortuitous circumstance some cell divided but the daughter cells did not separate. Groups of cells then specialized, each along essential lines for the most efficient acquisition of each of the factors essential for its specific energy —sunlight and oxygen. Thus through constant changes, as the result of fortuitous circumstances, form after form was evolved, each becoming more complex as the range of responses widened. For the unified responses of the more complex mechanisms the bipolar arrangement continues to exist, positive electric forces becoming centralized in certain tissues and negative forces in other tissues until in the final form, in accordance with this conception, we conceive that the tissue of highest positivity is the brain and central nervous system while the tissue of highest negativity is the liver.

Just as in the single cell the differences upon which its life depends are due to the strain—difference in potential—between the positive pole—the nucleus on one side of the condenser plate, and the negative pole—the cytoplasm on the other side of the condenser plate, so in the multicellular organism the electric forces which maintain its varying activities are due to the difference of potential maintained between the central nervous system and the other organs and tissues.

That the brain and the liver are the organs in which are the centers of positivity and of negativity in the organism would appear to be attested by the facts that the removal of either causes an immediate physical and functional breakdown of the organism; that when either of these has failed there is no known substitute for its function; that clinical experience and experimental research alike show an essential inter-relationship between them which is manifested between no other organs or tissues of the body.

Moreover, and this is of prime significance, the brain, of higher animals at least, seems to be so constructed that it can hold in a static position molecules which are so arranged that they may be orientated by specific electric energy in such a way as to facilitate in one direction and retard in other directions the forces between the cells. Only by such an arrangement in the positive pole of an electric organism could the purposeful interchange of activations between the constituent parts be effected.

Moreover, by means of these patterns whereby action currents are facilitated, we may conceive nerve fibers were constructed whereby the electric energy between the brain and the muscles or glands is made effective. By means of similarly facilitated patterns also we may conceive that more complex relations between different sets of brain cells were established. The electrostatic arrangement in these highly specialized conducting paths would thus hold innumerable chains of molecules which would be so balanced electrostatically that each impulse that passed over them would change their orientation.

These electrostatic chains of molecules would tend to remain passively in each position until a different electric impulse forced them into a new position. We may conceive that in some such way as this the so-called higher psychic functions, memory, reason, and thought find their physical basis. On this basis we may conceive that the new-born child is unconscious because these electrolytic, facilitated pathways are not yet created.

Thus we conceive of the living animal organism as an electrolytic system of cells in suspension, among which in the relation of individual cells to each other and in the relations of groups of cells to other groups there exist infinite numbers of differences in potential which are made effective for the more adaptive reactions by means of nerve connections; and for the basic but less changing reactions by means of the electrolytic solutions in which the cells are suspended.

By means of these intricate condenser-oxidation-bipolar arrangements the infinite numbers of reactions which are manifested in growth and development are made possible, from the primary reactions of the ovum to the manifold reactions of movement, thought and memory in the adult individual.

Thus if our fundamental conception is correct, the bipolar theory relates the energy of the animal to the sun's energy. It assigns to oxidation its essential rôle of charging up the condenser films whereby the required differences in potential in the cells and in groups of cells are maintained from birth to death; it shows why, if oxidation is withdrawn for a few minutes, the brain cells lose their difference in potential—hence their ability to drive the organism—hence to maintain that state of activity which is manifested in consciousness. Since in accordance with this theory, memory and thought are dependent upon the facilitation of discharges of energy along selective paths, diminished oxidation would produce sluggishness of mental activity.

The bipolar theory explains why life exists only in water, water being a non-conductor, the oxidating property of which excels that of any other medium, and being also the only medium with which can be formed, from the common earthy salts, the electrolytic solutions essential to life, in which the cells—batteries—are suspended. This theory explains the rôle of the monomolecular lipoid membranes. It explains the primary importance of the acid-alkali balance in all living organisms. The bipolar theory shows that the living organism is a mechanism adapted to electric control, hence susceptible of being driven by trigger action by such minute forces as a beam of light, which by trigger action discharges relays of hundreds of thousands of cell condensers, causing a massive reaction which may involve the entire organism, just as the minute force conveyed by a wireless wave may explode a mine.

Even more readily the bipolar theory interprets the trigger action of the impact of sound waves, of physical contacts. It interprets the chemical action of the infinitely small particles which cause smell and taste. It interprets the chemical reactions of fever, digestion, and respiration; and it provides a possible interpretation of the processes of memory, reason, consciousness and sleep. It identifies the mechanism of fatigue, exhaustion and restoration, of surgical shock and its prevention. It interprets the action of adrenalin. It explains the rôle of acids and of alkalies in the organism. It explains the action of anesthetics. It interprets the rôle of various electrolytes. It

explains the prime importance of water for the maintenance of normal life and why water is the most potent means of restoration. It explains the rôle of the lipoid films. It explains why universal connections among cells and organs and among the dynamic units which are the basis of protoplasm are essential. It interprets the characteristics of protoplasm itself.

It provides the basis for the interpretation of the evolution of man through the ages since the first potential was created by sunlight between an infinitely small positive particle of matter of ultra-microscopic size and the common negativity of the electrolytic solutions of the sea or mud, through many forms and in constantly increasing complexities from unicellular organisms to multicellular organisms; passing through form after form; always becoming more complex until now the most complex animal organism—man—has become adapted to many of the forces of the earth and is reaching out toward the sky.

Whether or not man will evolve to higher levels or whether or not conditions will be unfolded which will defeat man's hopes and aims; whether we are passing through protracted phases of organic life as a whole to be followed by long periods of equilibrium and death, after which the process may or may not begin again, it is needless to speculate. The prime point in its relation to our theory is that in spite of the heights to which man has risen and to which we believe he is yet to rise, and in spite of all the infinite structures whereby that height has been attained, man has not changed from the primitive pattern of his primeval unicellular ancestor.

We concede that our thesis has not been finally proven. Final proof is lacking regarding practically every point. We concede that the bipolar theory would fail to explain living processes if any other form of energy than electric energy could be proved to be adapted to construct and to operate an organism which is identical with or analogous to that of the human organism.

Thus the electric or bipolar theory would be discredited if it could be shown that any life exists without electric phenomena, without oxidation, without water or electrolytes; if there were animals, the electric stimulation of the nerves of which would not make the organs supplied by those nerves perform their

normal function; if any higher animal were found that had no nerve cells and no liver, or if living tissue were found which showed no electric capacity; if the organism contained no accelerators or inhibitors of oxidation; if any other form of energy than electric energy could receive or react to such an infinitesimal force as faint light waves; if any other force could work continuously without intervals of inactivity—sleep; if any other force could be adapted to the instantaneous stepping-up whereby the massive reactions of powerful animals are released; if any other force should require for its operation such make-and-break mechanisms as the synapses, or an acid-alkali balance, or the division of the body mass into trillions of cells, or the presence everywhere of dielectric oil films 4/10,000,000 of a centimeter in thickness; if there were any other force whose action would fail to activate the organism if the brain and spinal cord were removed or the liver excised; if any other force would offer even a slight suggestion of the mechanism of memory; if any other force existed universally in the non-living as well as the living, thus revealing the link between the living and the non-living, and providing a plausible evolution from the non-living materials of which the organism is constituted to life itself.

If any other force such as heat or light or gravitation or intermolecular force or chemical action could so universally fit into the great scheme of the living and the non-living universe as does electricity, then the electric or bipolar theory of living organisms would be without foundation.

Since in its last analysis all matter is electric in nature and all force is convertible into electricity, it would indeed be difficult to find any other form of energy that could rationally form the basis of life. If life originated through the action of the forces which engulf us, then the one force that could conceivably account for the atom, the compound, the solution, the colloid, could surround particles of matter such as form the colloids with films, could aggregate and limit forces and forms from the minutest to the most massive, must be the universal force which is everywhere present, in every form of non-living and living matter from the atom to the man and makes of each a bipolar mechanism.

APPENDIX A

Citations from the Literature

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Citations from the Literature

It is obviously impossible even to approach an adequate summary of the literature pertinent to the various phases of the discussion in this monograph. The following citations from the publications of various investigators are made, however, because they offer striking evidence in support of various arguments presented in the text.

Light

Among the various phenomena which are discussed by Loeb, those of heliotropism are especially susceptible of an electrical interpretation.

"We must, therefore, conclude that the light produces in an eye or an element of the photosensitive skin a chemical reaction which results in the formation of a certain mass of a reaction product. This mass acts on the peripheral nerve endings and brings about an as yet unknown change in the brain elements with which these nerve endings are connected. This change in turn affects the tone or tension of the muscles with which the brain elements are connected. When the rate of photochemical reaction is the same in both eyes or in the photosensitive elements on both sides of the body, the change of tone in the symmetrical muscles of both sides of the body is the same and no change in the position or direction of motion of the organism should occur. If the rate of illumination is different in both eyes, differences in the relative tension of the symmetrical muscles occur, which make the motion to the source of light easy and in the opposite direction more difficult when the animal is positively heliotropic. For the negatively heliotropic animal the opposite effect will be brought about." (Loeb.)[1]

Heat

"Where is the heat before it appears as heat? Is it in the foods, or in the oxygen, and in what form is it? This was long a puzzling question and in some ways it still is puzzling. It may be answered tentatively and in part as follows: Both carbon and hydrogen have

a great attraction for oxygen. For some reason, not at present understood, an atom of oxygen and an atom of carbon in certain conditions attract each other so strongly that to separate them much work is required. A similar attraction exists, also, between hydrogen and oxygen. Why the union between hydrogen and oxygen should be so much firmer than between other elements is not yet clear; but there is no doubt about the fact. When, therefore, they are separated, energy is consumed; and this energy is represented by the separate positions or distance apart of the atoms. It is energy of position or potential energy. It is supposed to be a condition of strain in the ether which fills all space. Light, working in the chlorophyll parts of plants, is able to bring this separation to pass. The light energy disappears and is represented by the potential energy of the system carbohydrate-oxygen. Now for some reason carbohydrate, which contains both carbon and hydrogen, does not combine readily with oxygen in spite of the great attraction between the oxygen and carbon atoms. It is as if there was some resistance in the way of their union; but under the conditions prevailing in protoplasm this resistance, whatever its nature, disappears, and now the carbon and oxygen atoms rush together with great violence, drawn by their mutual attraction. In the violence of their impact they rebound and vibrate vigorously back and forth. Sometimes this vibration is so fast and so vigorous as to give rise to light. This happens in the phosphorescent substances; in other cases the vibration is communicated to the surrounding molecules and is gradually dissipated in longer molecular vibrations, and this we call heat." (Mathews.)[3]

Interatomic, Intermolecular and Intramolecular Forces

Nernst's application of the osmotic theory to the mechanism of current-production in solutions referred to in the text is given in the following excerpt:

"In the contact between two solutions of an electrolyte of different concentrations, there is developed an electromotive force which so acts between them, that the one ion strives to pass by the other. In this way we obtained for the first time a mechanical explanation of the potential difference between any two substances, and it became possible to calculate this value in absolute measure. . . . We can explain mechanically in an entirely similar way, the potential difference occasioned by *the contact of the solutions of any two different electrolytes.*

"Thus let us bring into contact with each other a solution of HCl and of LiBr; then, on the one hand, more hydrogen ions than chlorin ions will diffuse from the first solution into the second, and there-

fore the second solution will receive a positive charge; and, on the other hand, more bromine ions than lithium ions will diffuse from the second solution into the first, because of the greater mobility of the bromine ions; and thus the positive charge of the second solution will be increased.

"Moreover, these electromotive forces can be calculated in absolute units of measurements, from the gas laws and the ion mobilities, for which purpose Planck has developed, by integration, the general equations given by me.

"In this way we have arrived at a general method for calculating theoretically the electromotive forces of any liquid cells, provided that only dilute solutions are used, by means of the gas laws and the ionic mobilities; and, moreover, the details of mechanism by which these batteries produce the current, are now perfectly clear. . . .

"The general principle by means of which, as we have shown in this chapter, we have calculated the potential differences between substances may be formulated as follows. We attribute to the ions the same properties as to electrically neutral molecules; if we now consider any phenomenon which involves a change of place of molecules (*molecular phenomenon*), then the same process applied to free ions will usually have the consequence of separating anions and cations; this causes a potential difference. We may, of course, calculate the latter if we know the laws of the molecular phenomenon in question. On account of the enormous electrostatic capacity of the ions the quantities that are actually separated are too small to weigh.

"Thus, for example, the theory of diffusion of non-electrolytes (a molecular phenomenon) leads to the theory of potential difference between dilute solutions, since the general laws of diffusion are applied to the diffusion of electrolytes (an ionic phenomenon). The comparison of the solubility of ordinary substances with the solubility of metals leads to the much used formula for the potential difference between metal and electrolyte. . . .

"We may well say that the osmotic theory has enabled us to give in many cases a thorough explanation of the mechanism by which current is produced, and that we have reached a general solution of the problem of calculating electromotive forces from other phenomena which are easily observed." (Nernst.)[8]

As for the osmotic pressure in colloidal solutions, Nernst makes the following pertinent statements:

"At present, when we can detect a 'head' of pressure directly from the phenomena of diffusion, we must in all probability suppose that there is no essential difference between solutions of colloids and of crystalloids. But the extreme slowness of the diffusion of colloids indicates emphatically two things: on the one hand, the driving force

must be very small, *i.e.*, the osmotic pressure is very small; and, on the other hand, the resistant friction experienced by the molecules in their passage through the water must be enormous; both these conditions are explained by the assumption *that the colloids possess exceedingly high molecular weights.*

"Now, as a matter of fact, the experiments conducted with colloid solutions show very small values for the osmotic pressure." [4]

Colloidal Solutions

The following excerpts from Loeb's "Theory of Colloidal Behavior" are especially pertinent to the electro-chemical theory of living processes: [5]

"Donnan has shown that when a membrane separates two solutions of electrolytes one of which contains one ion which cannot diffuse through the membrane while all the other ions can diffuse through the membrane, the result will be an unequal distribution of the diffusible ions on the opposite sides of the membrane. At equilibrium the products of the concentrations of each pair of oppositely charged diffusible ions are the same on the opposite sides of the membrane. This unequal concentration of the crystalloidal ions must give rise to potential differences and osmotic forces, and we intend to show that these forces furnish the explanation of colloidal behavior."

"In a preliminary note on his work on globulins published in 1903, Hardy gives an interpretation of the influence of H and OH ions on the direction of migration of protein particles in an electrical field which was destined to play an important rôle in colloid chemistry, since it suggested to the later workers that the H and OH ions produced their influence on the electrical charge of the protein particles through a process of adsorption. . . .

> " 'A precipitate of globulin is to be conceived not as composed of molecular aggregates but of particles of gel. I have shown elsewhere that gelation and precipitation of colloidal solutions are continuous processes. These particles of gel when suspended in a fluid containing ions are penetrated by those ions. Let the fundamental assumption be that the higher the specific velocity of an ion the more readily it will become entangled within the colloidal particle. Then as H and OH ions have by far the highest specific velocity the colloidal particle will entangle an excess of H ions in acid and thereby acquire a + charge and of OH ions in alkali and thereby acquire a — charge. These charges will decrease the surface energy of the particle and thereby lead to changes in their average size.'

"Perrin adopted the idea that H and OH ions confer their electrical charge to colloidal particles on account of their relatively large velocity of migration, whereby they were readily adsorbed by the colloidal particle. The hypothesis of a preferential adsorption of H and OH ions by colloidal particles has since played a great rôle in colloid chemistry.

"In 1904 the writer of this volume offered instead of this colloidal a purely chemical view of the significance of the isoelectric point and of the cause of the influence of acids and alkalies on the direction of the migration of the colloidal particles.

> " 'It seems to the writer, however, that a different view of these phenomena is possible whereby they appear in harmony with the view of electrolytic origin of the charges of colloids. The proteids are known to be amphoteric in their reaction. If they be slightly dissociable they will send H as well as OH ions into the solution. When the particles send more H ions than OH ions into the solution they will have a negative charge while they will have a positive charge when more OH ions are given off than H ions. If acid is added to the solution in sufficient concentration the amphoteric colloidal particle will send more OH ions into the solution than H ions and hence, will assume a positive charge. The reverse will be the case in an alkaline solution. It harmonizes with this idea that, as Hardy found, neutral salts do not influence the sign of the electrical charge of the globulins.' "

"We may consider a protein solution inside a collodion bag and surrounded by a watery solution as a model of a protein micella suspended in a watery solution. In that case it can be shown that the electrical charge of such a model varies in exactly the same way as the charges of colloidal particles in suspension, *e.g.*, coagulated egg albumin.

"1. The electrical charge of the micella model (*i.e.*, gelatin solution in a collodion bag) is zero at the isoelectric point.

"2. The charge of the model is positive on the acid side and negative on the alkalin side of the isoelectric point of gelatin and of crystalline egg albumin.

"3. The charge of the model increases with the addition of little acid and diminishes with the addition of more acid to isoelectric particles.

"4. The charge of the model is diminished by the addition of low concentrations of neutral salts, and the depressing action of the salt increases rapidly with the balancing of that ion of the neutral salt which has the opposite sign of charge to that of the micella.

"It has been shown in the preceding chapter that these facts can be explained not only qualitatively but quantitatively from the theory of Donnan's membrane equilibrium. This quantitative agreement

leaves no doubt that the electrical charge of this micella model is caused exclusively by the Donnan equilibrium."

"In Hardy's experiment with white of egg the particles were positively charged on the acid side of the isoelectric point and negatively charged on the alkaline side. It can be shown that this is also true for the charges of the suspended particles of powdered gelatin, and that this change of sign of charge of these particles by going from the acid to the alkaline side of the isoelectric point is accompanied by a change in the sign of the value (pH inside micellæ minus pH outside)."

In the same volume Loeb offers the following discussion of "the origin of the electrical charges of living cells and tissues":

"In his first paper on the theory of membrane equilibria Donnan suggested that the membrane potentials postulated by his theory might contribute towards an explanation of the action of nerves and even of electrical fish. In 1911 the writer suggested to Dr. Beutner that he investigate the P. D. between such organs as apples, or leaves of the rubber plant, and water, instead of the P. D. of muscles or nerves, which had usually been used by physiologists for this purpose. In these experiments Dr. Beutner made the important observation that the P. D. between the surface of an apple or a leaf was a maximum, when the bounding liquid was pure water, while the P. D. was depressed when a salt was added to the water, the depressing effect on the P. D. increasing with the concentration of the salt. MacDonald had observed a similar phenomenon, namely, the increase in P. D. between nerve and surrounding salt solution with increasing dilution. Donnan's theory was not known to us and we were not able to give an explanation of the depressing effect of salt on the P. D.

"A search was made for those substances in the cortex of an apple or leaf which might be responsible for these peculiar concentration effects on the P. D. When the P. D. between solid gels of gelatin and of coagulated egg albumin and water was investigated, no potential differences were observed, to the great surprise and disappointment of the writer, who had hoped that the investigations of the P. D. might lead to an explanation of the antagonistic ion effects in which he was then interested. It is possible that the negative results with protein were due to the fact that the measurements were accidentally made near the isoelectric point. On the other hand, it was found that there existed a P. D. at the boundary of lipoids (lecithin dissolved in guaiacol) which was depressed by the addition of salts and the more the higher the concentration of the salt.

"This analogy between lipoids and living cells gave us the impression that the proteins had no share in the potential differences observed between living tissues or living cells and watery solutions.

The experiments recorded in this chapter leave no doubt that this conclusion was wrong; any ion in a cell or on its surface which cannot diffuse into the surrounding watery solution (no matter whether the ion is a protein or a fatty acid or some complicated lipoid or a complicated carbohydrate or even a crystalloid) can or must give rise to a P. D. which is depressed when a diffusible salt is added to the surrounding watery solution.

"The idea that lipoids are the substances responsible for the P. D. of tissues led Beutner to an extensive and most interesting investigation of the P. D. at the boundary of water-immiscible substances and water. He found always a depressing effect of the addition of salt. Beutner tried to explain this on the basis of differences in the electrolytic dissociation in the watery and the water-immiscible (oily) phase. Such an explanation cannot be applied to the experiments with protein solutions and yet these latter solutions also show the depressing effect of the addition of salt on the P. D. in a most striking way. In this latter case the depressing effect of the salt on the P. D. is due to the Donnan equilibrium, and there is no reason why the theory of membrane equilibria should not apply to the P. D. between oily and watery phases, since this theory only demands that one ion of the oily phase should be prevented from migrating into the watery phase. Any lipoid ion would fulfill this postulate of the theory. The peculiarities of electrolytic dissociation found by Beutner in non-aqueous solutions must, however, influence the Donnan equilibrium in a secondary way, since this equilibrium depends upon ionization."

Oils and Fats

Ivanow's conclusions regarding the reversible action between carbohydrates and fatty acids is cited by Haas and Hill: [6]

"Ivanow considers that there is no real difference between the saturated and unsaturated fatty acids in their power to give origin to carbohydrates. The difference in their amounts is due to the more rapid conversion of the unsaturated variety. However this may be, the salient feature in the germination of a fat-containing seed is the conversion of the fat into carbohydrate, the reverse to what obtains during the maturation of the seed. The change is affected by the activity of lipase which hydrolyses the fat into glycerol and fatty acid.

"The work of Ivanow has shown that lipase has a reversible action, and the fact whether it hydrolyses or synthesizes fats is merely a question of conditions, mainly the presence or absence of water. The glycerol extract of a fat-containing seed, which extract contains the lipase, mixed with oleic acid will synthesize a fat: the addition of

water will result in the hydrolysis of this fat into glycerol and fatty acid. . . .

"With regard to the origin of glycerol, the chemical relationship between this substance and glucose is so close as to suggest at once the possible inter-relation of the two; further, glycerol may have an origin in respiratory processes as is shown by the production of this substance during the alcoholic fermentation of sugar."

Central Nervous System

Many excerpts from the monumental work of Cajal might be cited. Indeed his description and drawings of the histology of the central nervous system strongly corroborate the theory that electricity is fabricated in and transmitted by the central nervous system. In many instances, Cajal suggests an electrical interpretation of nervous function.[7] Thus in discussing the spinous processes on the protoplasmic appendages of the brain cells the author states that when stained by Ehrlich's method the terminal spherule stains an intense blue like the protoplasm of the cell. In considering the function of these appendages, he says:

"What can be the rôle of these collateral processes? At present, we do not know. They might be considered as absorbent hairs, like the radicles of plants, as suckers, securing in the peri-nervous lymph the organic juices for the nourishment of the spongioplasm of the dendritic arborization. Or are they, as Berkley maintains, charging apparatus, the collectors of the nerve current, like the points of a static electric machine or the brushes of a dynamo."

Cajal agrees with this latter opinion and calls attention to the enormous increase of surface thus established.

His theory regarding interneuron communication to which we have referred in Chapter V is stated as follows:

"The protoplasmic prolongations, the cylinder-axis extension and the cellular body are free, and nevertheless throughout the nervous system thus divided and infinitely interrupted, the currents circulate unceasingly. How can they pass? Only one answer is possible, by contact, like electric currents through a wire. But the nerve extensions, the protoplasmic appendages, the cellular body—all this in the gray matter for example, is mingled, entangled, in more or less intimate contact. In this labyrinth do the effector and affector currents pass indifferently, without order, from one cell body to

another cell-body, from one dendrite to another dendrite, from one nerve extension to another nerve extension, or from one of these three parts of one cell to any other of the three parts of another cell? Or is there, on the contrary, a well-established law which fixes the parts of the cell which should enter into contact with each other?

"All the mechanism of the nervous system proves that this last supposition is the true one and that such a law exists. Our investigations have made it possible for us to identify this law. It is this: *The articulation or useful and efficacious contact between two neurons is only effected between the collateral cylinder-axis ramifications or terminals of one neuron and the protoplasmic extension or body of another neuron;* or otherwise expressed, the nerve wave passes by contact from the axillary ramifications of one cell to the body and dendrites of another or other cells. At the beginning of our researches we believed in the existence of contacts between the dendrite extensions springing from one or more cellular elements. That which made possible the existence of these dynamic communications was their limitation to a colony of neurons the functional activity of which thus combined offered something comparable to that of a battery of piles or of Leyden jars. But these protoplasmic juxtapositions have not withstood later and more meticulous investigations. They are in any case extremely rare and lack, we are persuaded, any important physiological signification. The interposition of multitudes of nerve fibres or of expansions of epithelial corpuscles carefully prevents contacts between appendages of the same kind. Similarly there are possible contacts between extensions of different kinds but emanating from different cells which for especial reasons have not entered into connection. The neuroglia prevents this as best it can. The measures taken by nature in these two instances explain a fact demonstrated recently by Weigert thanks to a special method. We refer to the relative abundance of neuroglia fibrillæ in the region of the gray matter, molecular layers of the cerebrum and cerebellum, the superior olive, molecular layers of the retina, etc., where in large numbers are found demyelinized protoplasmic extensions and axis-cylinder arborizations. On the other hand at the level of the surface of charge, at the points of transmission of the current, that is to say, in the regions where the cell bodies and the dendrites acquire intimate relations with the ultimate ramifications of the axone—in all these regions the neuroglia is completely lacking. Thus by this ingenious artifice of the neuroglia, properly interpreted, we have again, if it is necessary, a confirmation of the law formulated above.

"It is then well-established, at present, that between the different parts of two or more neurons only one articulation is possible and valid—the articulation nervous-protoplasmic.

"But under what aspects does this articulation present itself? In view of the extreme diversity of the contours and directions of the

cellular parts, this articulation cannot be uniform. Yet in accordance with the law which governs nerve connections we can distinguish two grand divisions: the first in which the articulation is made between the arborizations of the cylinder axis and the body of the cells, called *axo-somatique;* the other in which the contact is between the cylinder axis arborization and the dendrite prolongations —*axo-dendritique.*

If we interpret this *axo-somatique* connection between the cells as analogous to the wiring of a battery in series, it becomes necessary to discover evidence that one or the other of the cell appendages is connected, at least at the moment of discharge, with the membrane of the nucleus, the other with the membrane of the cell body. Magini's experiment already cited (p. 66) becomes of very great significance in this connection. It is described by Cajal as follows:

"Magini carried his researches to studies of the changes in the position of the nucleolus according to the physiologic state of the neurons. As the object of his study he chose the cerebro-electric lobe of the torpedo. He believes that he observed the following phenomena; that the nucleolus occupies in periods of rest a central or slightly eccentric position in the nucleus; in periods of activity, it quits its position, moves rapidly in the direction of the axone, and applies itself so vigorously against the membrane of the nucleus that it produces a protuberance. According to Magini, the cylinder axis springs from the cytoplasm at a point near the protuberance produced in the nuclear membrane by the nucleolus. The rapid displacement of the nucleolus would result in striking against the cylinder axis and developing in it a nervous wave which would discharge the electric organ.

"If this interesting phenomenon should be confirmed, if moreover its existence should be proved in the cerebrospinal axis of all the vertebrates, one could affirm that the discovery of Magini truly constitutes a great progress in our knowledge of the physiological mechanics of the cell."

Cajal states that Vas, Lambert and Mann all observed this eccentric position of the nucleus but that Valenza denied all these findings, and also those of Hodge, Mann and Lugaro regarding the changes in the nucleus in activity and fatigue.

The nuclear origin of the neuromotor apparatus of certain unicellular organisms as described by Kofoid and his associates appears to supply a link between the undifferentiated nucleus of the simplest protozoa and the highly differentiated nervous sys-

tem of the multicellular organism and thus supplies further evidence in favor of the conception that the central nervous system of man is in truth the direct descendant of the nucleus of the original unicellular organism. [8]

"The term neuromotor apparatus is used by us here and elsewhere to designate those organs of the protozoan body which carry on its coördinated motor and locomotor activities. They form a structurally continuous unit as shown in *Trichomonas* and *Giardia* connected by a rhizoplast with the nucleus as in *Trichomonas,* or with the central karyosome as in *Giardia.* On maceration of the cytoplasm in *Trichomonas* and *Trichomitus* this apparatus remains structurally intact for some time. It includes in *Trichomonas* the following structures: The anterior flagella, marginal filament of the undulating membrane, posterior flagellum, axostyle, parabasal body, blepharoplast, and rhizoplast. In *Giardia* there are added the anterolateral, posterolateral, and free ventral flagella and an axostyle terminating in the posterior flagella, the intracytoplasmic parts of the first two pairs of flagella just named, a rhizoplast going from the parabasal body presumably to the blepharoplast, and a cross commissure joining the right and left blepharoplasts. The integration of these parts in one coherent structural system and its intimate relation to the mobile cystostome are evident on an inspection of the figure. (See Fig. 25.) The repeated instances of the attachment of the blepharoplast to the nuclear membrane by a rhizoplast in the various flagellates which we have discussed and the direct connection of the neuromotor apparatus with the karyosome of the nucleus in *Giardia* give presumptive evidence of a fundamental structural and functional relation between the nucleus and this complex of extranuclear organelles. The fact also that the blepharoplast and its outgrowths and connections are basophile and stain more or less deeply with iron haemotoxylin suggests affinities if not similarities, of a chemical nature.

"Added ground for regarding the extranuclear neuromotor apparatus as related to the nucleus and as evolved and derived from it is to be found in the results of Dr. C. W. Wilson's (1916) study of the life history of a soil amoeba, *Naegleria gruberi.* This amoeba enflagellates on the impact of various environmental factors such as access of oxygen, or of fresh culture medium, and exflagellates with equal facility. In the amoeboid phase there is no extranuclear blepharoplast, rhizoplast, or flagella, and no chromatic extranuclear organelles, though chromidial formations are abundant and varied at times in the life history. As enflagellation approaches a chromatic process grows out from the central karyosome of the nucleus forming an intranuclear rhizoplast extending to the nuclear membrane. A granule appears at its tip and as this process continues its growth peripherally through the cytoplasm, retains its terminal position until

it reaches the surface where it forms the blepharoplast connected on the one hand with the nucleus and on the other giving rise to the two flagella. In exflagellation the flagella shorten and fusing with the blepharoplast and rhizoplast appear to retreat again into the nucleus. In this connection we note the fact that no instances of mitosis were discovered in the flagellate phase, though they are to be expected, and in consequence we do not know the behavior of these organelles in that process. The centrosome or centriole is contained within the karyosome and appears here as in other amoebas at mitosis, at the ends of an axial chromatic thread in the center of the nuclear spindle. Thus in this amoeba the centrosome within the central karyosome of the nucleus originates the extranuclear neuromotor apparatus of the flagellate stage." (Kofoid.)[8]

"The first point favoring the idea that the neuromotor apparatus is of a truly nervous character comes from animals stained with Mallory's connective-tissue stain. In animals treated with this combination of dyes, different organs take different colors. It is characteristic in metazoan tissues treated by these colors for different tissues to stain differently, as for example nerve fibers have an affinity for acid fuchsin and are thus dyed red while nuclei stain orange red, and cytoplasm in general becomes light pink. Such a differential stain may be used to give a clue to the function of organelles in some of the more complex of the so-called unicellular organisms. At least we may assume that structures having a similar staining reaction have the same or related chemical composition and in these so-called simple organisms probably the same general function.

"This is one of the reasons for basing our conclusion that the structures described as comprising a neuromotor apparatus are probably nervous in their function. All of the fibers, granules and motorium stain bright red when treated with Mallory's stain, while the other structures take other colors. The only other organ which constantly stains with acid fuchsin is the micronucleus, but in this the color is not the same as in the fibers but has more of the orange G mixed with the red." (Yocum.)[9]

The Liver

The studies by Renauld-Capart cited in Chapter VI are of especial note in their relation to the essential interrelationship of the brain and the liver. By what he terms the "method of partial circulation," the general circulation was as far as possible confined to the brain, the heart being conserved as a motor and the lungs as an apparatus for oxygenation. After a longer or shorter time function of the nervous centers ceased, and then by admitting the blood from different abdominal organs it was possible to discover which of these had any influence upon cerebral activity.

"The first fact established was that the abdominal blood is essential to the function of the brain centers. This being demonstrated we directed our research to discover which of the abdominal organs could so affect the blood as to influence the cerebral activity. We have from the very first established that the blood which passes through the liver has the property of reëstablishing cerebral function; following this, that the liver alone, of all the abdominal organs, has that property.

"This being true, a new problem arose. With what action has one to deal under these conditions? Is it an action of 'desintoxication' or an internal secretion of nutritive material indispensable to the cerebral function? We have demonstrated that the action is not one of 'desintoxication' but of an internal secretion of the liver and that this consisted notably in the elaboration of a thermolabile compound without which cerebral activity is impossible. We suppose that this compound belongs in the category of ferments or catalyzers without being able to make any more precise statement regarding it.

"We then extended our research to determine what was the action of this function of internal secretion of the liver on the physiology of the neuron and particularly on its irritability. We have established that the arrest of the hepatic function produced in the neurons a state of chromatolysis which became more and more marked progressively with the loss of cerebral activity; and on the other hand, that its reëstablishment produced a demonstrable repair of the chromaphil substance corresponding to the re-appearance of the functions of the brain centers. We have also had the opportunity to observe the physiologic rôle of this substance, which we consider to be the main support of functional nervous energy. We have found that the formation and the restoration of the chromaphil substance depends on the presence in the blood of the thermolabile principle secreted by the liver. Finally, we have secured proof that cerebral work, including the highest form of conscious 'sensibility' is absolutely dependent upon this new internal secretion of the liver." [10]

Granting the correctness of Renauld-Capart's results another interpretation is possible. The author, by cutting off the circulation and oxidation of the liver, interfered with its fundamental activity sufficiently for its function as a negative pole to be suspended, and on the restoration of its circulation, the liver resumed its function as the negative pole of the bipolar organism.

The tendency of the liver cells to accumulate mineral substances —especially metals, is emphasized by Roger: [11]

"There is no ground for believing that the liver arrests indiscriminately every substance brought to it by the portal vein. It exercises

an elective action which is very clearly demonstrated by a study of the mineral salts.

"Many of the mineral poisons are accumulated in the liver. Some are eliminated by the bile. Others freely pass through the gland. Thus the liver has no action on chlorid of potassium or on the chlorid and the lactate of sodium. On the contrary it takes up the iodids and the bromids and eliminates part of them by the bile. By the same route it throws off ferrocyanid of potassium and sodium salicylate.

"The action of the liver is especially marked on the heavy metals. Lactate of iron is only one-third as toxic when it is injected through a branch of the portal vein as when it is introduced by a peripheral vein. Under the same conditions the albuminate of copper loses half of its toxicity.

"On the other hand, the liver stores and holds for long periods the salts of mercury, of lead, of arsenic. It eliminates a small quantity of these salts by the bile. The salts of manganese, of antimony, of silver, of zinc also are eliminated by this secretion.

"It is now generally accepted that the accumulation of the heavy metals is due to their combinations with the nucleus. According to Siccardi and Roncato in dogs subjected to lead poisoning, the lead is reduced and remains in its metallic state in the cells of Kupffer. Moreover these anatomical elements seem to have the property of retaining many substances foreign to the organism. Thus Kupffer has shown that after the injection of India ink in the veins of a rabbit, these cells become engorged with black grains. Colin and Nathan made analogous observations with colloidal silver. Duhamel has made comparative studies of several metals or metallic colloids. In less than 15 minutes after the injection of 0.0125 kg. of colloidal platinum in the veins of a rabbit, the cells of Kupffer are filled with metal. With colloids of copper, of mercury, of selenium, of iron, of sulphur, the results are negative or at least a histochemical examination does not make it possible to find the introduced substances. But chemical analysis gives different results. Here, for example, are the tables given by Duhamel; the studies were made 15 minutes after the injection.

SUBSTANCE INJECTED	QUANTITY INJECTED GRAMS	QUANTITY FOUND IN		
		LIVER	KIDNEYS	SPLEEN
Silver	0.018	0.012 (66%)	0	traces
Platinum	0.0125	0.0084 (67%)	0	"
Selenium	0.0125	0.0076 (60%)	traces	0
Mercury	0.01	0.0065 (65%)	"	traces
Copper	0.0125	0.0053 (42%)	"	0
Iron	0.05	0.028 (36%)	"	"

"Thus about two-thirds of the quantities introduced are very rapidly accumulated in the hepatic parenchyma."

Misk [12] has reported that tin is found in normal human organs in the following proportions:

Liver and spleen	62.4%
Brain	1.4
Kidneys	4.6
Heart	1.8
Lungs	5.4
Stomach, intestines and contents	24.4

The amounts per kilogram of the fresh organs were as follows:

Liver and spleen	49.3%
Brain	2.1
Kidneys	1.2
Heart	5.6
Lungs	9.3
Stomach, intestines and contents	32.5

The fact that in each of two fetuses examined by Misk only a trace of tin was found in the spleen makes it appear that the percentages given above for liver and spleen pertain primarily to the liver.

Bodansky [13] and Thudichum report studies which indicate that copper is a normal constituent of the brain. Bodansky's experiments indicate that this is true also of zinc. Regarding the presence of the latter metal, however, there appears to be a difference of opinion among various investigators. It is interesting to note, however, that in fetal brains the proportion of copper was greater than in any of the adult brains studied and that in general there is a more rapid accumulation of zinc and copper in the organs during intra-uterine life, as is also reported by Maquenne and Demoussy (noted by Bodansky) who "found in their studies on the injection of copper in the tissues of green plants that copper is most abundant in young actively growing tissues."

Muscles

We have already referred to the extensive studies (Chapter V) in muscular function made by Hill and Hartree.[14] Of particular interest from the bipolar point of view is their analogy between the

energy exchanges in muscle and in an electromagnet although we note that they state that

"this is not a theory of contraction, but merely a physical analogy to what has already been proved in regard to the muscle and its energy relations. The analogy is a very close one, and a close analogy may be valuable in suggesting lines on which further progress can be made, as well as in showing that a certain type of mechanism is possible.

"Consider an electromagnet attracting a piece of soft iron. To make the magnet exert this attraction a current has to be passed and energy has to be expended in magnetizing the electromagnet; to maintain the attraction it is necessary to maintain the current and the expenditure of energy. On breaking the current in the electromagnet the attraction disappears, while the magnetic energy of the electromagnet and of the magnetic field vanishes as such and reappears as heat caused by induced currents. Suppose further that the current was obtained from an accumulator: in order to recharge this accumulator it is necessary to employ some kind of engine to turn a dynamo and in this recharging process heat is liberated in the engine and 'free' electric energy is stored in the accumulator.

"*Store of free energy capable of being liberated without oxidative changes.* The accumulator can have its energy released merely by pressing a key and making an electric contact, just as the muscle can have its energy released by giving it a shock. The chemical changes liberating the energy of the accumulator do not involve any oxidative breakdowns, just as the initial processes of contraction in the muscle do not. The energy of the accumulator may be liberated largely as mechanical potential energy or work, or on the other hand if the accumulator be short-circuited it may be wasted as heat: the muscle's internal energy similarly may appear as potential energy or work or it may as a result of various conditions, *e.g.,* in rigor or as a result of treatment with ethyl-alcohol (Weizsäcker) appear entirely as heat.

"*Trigger action for release of energy.* The amount of energy required to make an electric contact and so to start the discharge of the accumulator is very small, as is the amount of energy required to stimulate a muscle.

"*Development and maintenance of mechanical response.* Directly the key is pressed down the current starts in the coil of the electromagnet and the magnetic attraction develops. The current, however, does not immediately rise to its full value, owing to the self-induction of the coil nor does the soft iron of the magnet become magnetized instantaneously under the influence of the magnetic field of the coil: hence the attraction exerted by the magnet on the piece of iron increases gradually up to a certain limit and then remains con-

stant: these phenomena are similar to those shown by a stimulated muscle. Moreover if the current be left on too long the accumulator becomes polarized, the current falls off and the magnetic field decreases: while if the accumulator be given a period of rest it recovers and provides its full E. M. F. again, and the magnetic field rises to its previous value. The phenomena of muscular fatigue are analogous.

"Disappearance of mechanical response. On opening the electric circuit the magnetic field of the electromagnet diminishes rapidly though not instantaneously to zero, and the pull on the piece of iron falls off. This process is analogous to relaxation.

"Performance of work. The current in the electromagnet develops a store of magnetic potential energy in the soft iron core and in the field round it. This magnetic energy will do external mechanical work, if allowed, by pulling up the piece of soft iron to the magnet. On the other hand no external mechanical work is done if the piece of iron be held fast. In the same way the muscle develops elastic potential energy on excitation: this energy may result in external mechanical work if the muscle be allowed to shorten, but in an isometric contraction no external work is done. The work actually performed depends, in both cases, on the 'conditions of loading.'

"Heat liberated in the development of the mechanical response. The energy of the current passing through the electromagnet reappears in two separate forms: (a) in the magnetic potential energy of the field of the electromagnet, and (b) in Joule's heat liberated in the coils. If the current passes only for a very short time the main part of the energy appears first in the 'free' form (a); while if it passes for a longer time an increasing fraction of it appears in the 'bound' form (b). Similarly with the muscle, energy is liberated (a) as mechanical potential energy and (b) as heat, (a) being the greater in a short response and (b) the greater in a long one.

"Heat-production in the maintenance of the mechanical response. In order to maintain a constant magnetic field a constant current has to be maintained in the coils of the electromagnet, the whole of the energy of which is degraded into heat. This is analogous to a tetanic contraction.

"Heat produced in the disappearance of the mechanical response. When the electromotive force in the circuit of the electromagnet is removed the potential energy of the magnetic field disappears in the process of inducing a current in the coil of the electromagnet or in neighboring conductors, the energy of this current being dissipated finally as heat. Thus, when we remove the E. M. F. exciting the electromagnet there is not a cessation of the heat-production; the heat-production continues until the whole of the magnetic energy of the field has been dissipated as heat through the intermediation of induced currents. Similarly in the muscle, as shown in this paper, when the stimulus ends the heat-production does not stop at once:

it continues until all the elastic potential energy of the muscle has disappeared.

"The recovery process. The whole of the phenomena described above are independent of the immediate presence of oxygen. When however it is required to recharge the accumulator an engine is started up, oxygen and fuel are consumed, heat and mechanical energy are liberated, a dynamo is turned and current is produced. Similarly in the muscle, when recovery is necessary some mechanism removing lactic acid is set in motion, oxygen is consumed, heat is produced and the muscle is restored to its previous condition.

"The heat produced at rest. It is known that accumulators left standing 'run down' gradually of themselves. This process of 'running down' must liberate heat, and if the accumulators are to be kept in condition it is necessary to recharge them. This continual recharging also involves a production of heat. Similarly, the muscle even when kept in oxygen-free atmosphere at rest liberates heat (together with lactic acid) continuously for long periods: if sufficient oxygen be present the running down process is balanced by a continual recharging one with an increased production of heat.

"The maintenance of tension in an unstriated muscle. Some unstriated muscles can, unlike the striated ones, exert a considerable tension for long periods without any appreciable increase in the CO_2 output. This fits into our analogy if we suppose that the core of the electromagnet is made of hard steel instead of soft iron, so that the magnetic pull is maintained with no further expenditure of energy until a current is sent into the electromagnet in the opposite direction to demagnetize it."

What Hill and Hartree express as an analogy we conceive to be an identity.

Reproduction and Cancer

The variations in the nuclear-plasma relation which accompany cell division have been analyzed by many biologists and various theories as to their significance have been offered. Many of these are summarized by Robertson in his monograph on "The Chemical Basis of Growth and Senescence," from which the following excerpts are taken:[15]

"It has been shown by R. Hertwig that immediately after the conclusion of cell-division a slight diminution of nuclear volume occurs which is succeeded by a slow and almost uniform rate of growth which is termed by Hertwig the 'functional growth' of the nucleus. During this phase of nuclear growth the cytoplasm grows both abso-

lutely and relatively more rapidly than the nucleus. This is succeeded by a phase of extremely rapid nuclear growth, termed by Hertwig 'divisional growth' during which the nucleus increases in volume at a relatively greater speed than the cytoplasm. In this way the ratio of nuclear to cytoplasmic material which obtained at the preceding division, the 'kernplasma-relation' of Hertwig, is regained and at this moment cell-division normally recurs.

"All observers are agreed that the most rapid nuclear growth occurs shortly before mitosis. The rate of nuclear growth therefore undergoes acceleration as it proceeds. The velocity of cytoplasmic growth, on the contrary, is comparatively uniform. . . .

"The kernplasma-relation is by no means constant in the different cells comprising an organism, or in unicellular organisms under varying environmental conditions. Thus Conklin, who agrees with Hertwig that 'the growth of the nucleus is more rapid in the last stage of the resting period preceding mitosis than at any other time in the cell cycle,' finds that the kernplasma-relation is extremely variable even in the earliest stages of embryonic development and Popoff has shown that by exposing infusoria to low temperatures abnormally high kernplasma-ratios may be obtained. We shall revert to the significance of these variations of the kernplasma-relation in later chapters, but for the present the fact which claims our attention is the autoacceleration which the growth of the nucleus displays, in contrast to the comparatively steady rate of accumulation of cytoplasm. Evidently we must infer that the whole of the accelerative agent is not shed from the cells into the medium which bathes them, but that a portion is also resident within the nucleus.

"There is also an entirely independent reason for ascribing the source of the autocatalyst of cell-multiplication to the nucleus. This is the fact, the experimental evidence of which will be described later, that the accelerative agent is only shed from cells into the pericellular fluid at the moment of division, when the nuclear membrane has been dissolved. The fact that it is shed at this period leads us to infer that no obstacle exists to prevent its issuance from cytoplasm, yet in the interdivisional periods it does not escape at all. Evidently, therefore, it is not present in the cytoplasm during the interdivisional period (at least in the necessary excess to permit issuance into the pericellular medium), and it must be prevented from escaping from the cell by the membrane which encloses the nucleus during this period.

"It is to the nucleus, therefore, that we must look, alike for the source of the accelerative agent in cellular multiplication, and the source of the autocatalytic time-relations which distinguish all types of growth. With certain special exceptions, such as the maturation of ova, or spermatogenesis, or the occasional formation of polynuclear cells, the growth of cytoplasm is determined by the multiplication of nuclei, for the obvious reason that nuclear division pre-

cedes and determines the moment of cellular division, and the subdivision of protoplasm ensures the accessibility of nutrients to all its parts and hence the uninterrupted growth of cytoplasm. Thus, if the production of nuclear materials in a multicellular organism or a culture of unicellular organisms is autocatalyzed, then the total production of protoplasm must similarly display autocatalytic time-relations."

Loeb and Osterhout have both shown that the nucleus is primarily concerned in the variations in oxidation within the cell, especially in the processes which are controlled by fertilization.

Ewing gives a valuable discussion of the relation of tumor cells to sex cells: [16]

"The abnormal capacity for growth has long suggested that tumor-cells have some *relation to sex cells.* In some animals the entire series of sex cells from the fertilized ovum up to the new egg cell has been traced as a distinct series apart from the somatic cells. In this series the mitotic nucleus exhibits only one-half the usual number of chromosomes, and these instead of assuming a V shape and radial arrangement are ring or loop shaped or composed of coarse granules. This gametogenous mitosis has also been observed in the growing edges of tumors (Farmer, Moore, Walker) and it may be produced by chemical irritants. Its occurrence does not signify that tumor-cells are equivalent to sex cells, and yet in connection with the invasive properties and striking altruistic relations of both classes it shows that tumor-cells and sex cells have some interesting points of resemblance. Spencer, Hertwig, and others claim that the sex potencies of somatic cells are not lost, but only suppressed. On this basis Williams has built an elaborate and ingenious argument to show that tumor growth signifies the reawakening of the reproductive functions in the somatic cells. According to this theory tumor growth is a form of agamogenesis comparable to the budding of plants.

"Many have supposed that tumor-cells are *fertilized cells,* through conjugation with leukocytes (Klebs), by parthenogenesis (Waldeyer), by conjugation of endothelium and fibroblasts (Recklinghausen), by nuclear conjugation (Auerbach, Bashford), or by endogenous cell infection.

"None of these hypotheses has survived criticism and the theory of cell autonomy remains content in the position that tumor-cells emancipated from growth restraints are merely exhibiting their natural capacity for growth."

In considering the "nutrient level in relation to growth" Robertson cites the work of certain investigators in support of a conception which is especially pertinent to our own discussion. Many

investigators have found that in starvation the cytoplasm of the cells is primarily affected, the nuclei being not reduced in size; that even with rupture of the cell boundaries the nuclei remain comparatively undisturbed; moreover

"It has been observed by Morgulis that there is a great acceleration of growth-rate in salamanders after a period of inanition. This may be most strikingly demonstrated by comparing the proportion of the food intake which is converted into protoplasm before and after a period of inanition. If at a certain period of growth the proportion of food converted into protoplasm was 26 per cent, after starvation and the readmission of food it rose to as high as 73 per cent. He states that 'it is possible that the reduction in size of the cells, or rather the diminished ratio between cell and nucleus, has something to do with the observed processes of intense growth, and that the rejuvenescence of the organism is analogous to the condition in the embryo, where the cell-body is likewise small in relation to its nucleus.' " [17]

Robertson extends his conception of the vital influence of the nuclear-plasma relation on the cells of the organism to the development of cancer as follows:

"Normally the degree of differentiation attained in the repair of lost or injured tissue does not exceed that which is still subject to control by the competition of adjacent cells, and the prevailing accumulation of autocatalyst. But this process, if repeated again and again, becomes virtually a process of selective breeding, whereby the cells of the lowest nuclear ratios are favored and enabled to propagate. Should the inherited variability of the cells in that locality enable, at length, the appearance of a type of cell so physiologically differentiated from its competitors, as to be able to multiply freely at the prevailing nutrient level, and in the presence of the prevailing accumulations of autocatalyst, then an outburst of reproductive activity must inevitably ensue, and the successful type of cell will inaugurate, if it is sufficiently differentiated, a malignant tumor. . . .

"The tumor, in the light of this hypothesis, owes its origin to an abnormal variability of the nuclear-cytoplasmic ratios in the tissues of the host. . . .

"Thus the development of cancer may be regarded as a phenomenon of hyper-differentiation of the cells of the host, brought about by repeated selection of types suitable for multiplication under conditions which inhibit the multiplication of cells of the host. The increase of autocatalyst due to the cells of the tumor itself must, however, render the nutrient medium even less suitable than before

for nuclear synthesis in the cells of the host, so that senescence of the host should be accelerated by cancer. This effect would be most intense locally and radiate outwards from the cancer tissue, forming an autocatalyst gradient descending from within outwards. The maintenance of normal nuclear ratios by the tissues immediately surrounding the tumor will thus be rendered more and more difficult. It is probably to this factor that the invasive quality of malignant tumors must be ascribed and its magnitude will depend simply upon the difference between the prevailing nuclear ratios in the adjacent tissues and the nuclear ratio which obtains in the neoplasm. As Whitman has pointed out, increase of the rate of multiplication of any tissue by itself would merely lead to hyperplasia and not to invasion and destruction of adjacent tissue. But if the rate of multiplication be sufficiently rapid then this second effect will supervene also and hyperplasia will be succeeded by invasion. For the same reason we can understand why cancer is so preëminently a disease of old age, because the increasing senescence of the normal tissues renders the advancement of their senescence to the point of incompatibility with life a comparatively easy matter, and their invasion by the tumor tissue is facilitated."

Robertson assigns to a hypothetical "nuclear autocatalyst" the function of maintaining the variations in nuclear-plasma relation which result in growth, cell-division, differentiation, etc. We assign the cause of these variations to variations in the energy—electric energy—which is the result of the essential bipolarism of the living cell.

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APPENDIX B

A Consideration of the Energy Transformations in the Body from an Electrical Standpoint

APPENDIX B

A Consideration of the Energy Transformations in the Body from an Electrical Standpoint

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There is considerable experimental evidence that impulses sent by the brain to the various organs and muscles of the body have an electrical character. These nerve impulses have been found to travel at the rate of 80 feet per second, which of course is much less than the velocity of electrical impulses along a wire or through space. If the speed 80 feet per second is correct, then the impulse along a nerve is not of the exact character of those along wires. Nevertheless one can well imagine a shift of electric fields by displacements of ions, which move at a velocity through solutions much slower than impulses along a wire.

The outstanding point to consider is that nerve impulses are electrical in character. The nerves have been found to be unaffected in temperature when impulses are sent along them, but one knows that the core of the nerve is a very good conductor. The amount of energy transformed to heat when small currents traverse this low resistance would be too small and perhaps too difficult to determine experimentally in a minute nerve structure. To repeat, the outstanding fact is that nerve impulses are electrical in character. Therefore there must be an energy transformation with the necessary condition that one of the aspects of energy has been electrical. In other words, to make possible and to give rise to these electrical impulses there must be a supply of electrical energy. Fundamentally a supply of electrical energy means a difference in potential, that is, a voltage.

* The author wishes to express his appreciation of Dr. Perrine's consent to the publication of this analysis of the bipolar theory from the point of view of a practical electrical engineer.

In every dynamic electric circuit, the discrete electrical charges must, in their coursing through the circuit, take on energy in part of the circuit, and give out energy in other parts. When these electrical charges are raised in potential, that is, pass from a lower to higher potential, that is, go from negative to positive, they take on energy. If the circuit is not closed, this passing from negative to positive potential stops very quickly, with the result that one has a static condition established, as in a dry battery not connected to any electrical device. If, however, there is a closed circuit, then in the external circuit, as one says, the electrical charges pass from a high potential to a low potential, that is, from positive to negative, and in so doing give out energy. This energy given out may result in heat, mechanical motion, or chemical decomposition. This means, of course, that the difference in potential originally established statically must now be maintained dynamically within the internal circuit, if there is to be a continuous energy transformation maintained. In the body the network of nerves corresponds to the external circuit, where energy is given out by the nerve to the muscle. This amount of energy is very small, and could be considered as a trigger to release a greater amount of energy in the muscle or the organ concerned. This trigger action, in which a small amount of energy releases a great amount of energy, that is, the nerve impulse having in it the concept of an amplifier, is a striking fact for consideration. The nerve impulses are sent out by the brain. Hence it is feasible to regard the brain as the positive pole of the battery. On account of conductivity and temperature experiments already performed together with the outstanding fact that a number of organs except the liver can be removed and life ensue, the liver can be regarded as the negative pole of the battery, that is, it is reasonable to consider that the liver is the only organ which is absolutely essential in the body's electrical circuit. The proposition is, therefore, that as long as there exists a potential between the brain and the liver, there would be available a supply of electrical energy from which the nervous system could get energy for its nerve impulses, and thereby life could be maintained. If there is no supply of electrical energy, that is, in electrical terms, if no potential exists between these two organs, then death ensues, since no stimulus could be given to any muscle or organ.

As previously stated, the fundamental fact to consider is energy transformation. The potential between brain and liver must not only exist, but must be maintained. This means energy must be supplied in either the brain or liver, or in both, in order to drive

electrical charges from negative to positive, thereby storing electrical potential energy. This energy could be very well supplied by the oxidation, which means a release of energy which takes place in these two organs. The oxidation which takes place in the cortex of the brain is greater per unit volume than anywhere else in the body. It would seem, therefore, that as a result of this oxidation in the brain, there could be a very definite rise in potential between certain parts of the brain structure itself. As stated above, oxidation means release of energy and this could be utilized to give an increased potential within the brain cells, that is, between the nucleus and its environs. It has been shown experimentally that within the cells of both the liver and the brain the hydrogen ion concentration differs very definitely in the nucleus and its environs. This would mean that there could exist a difference in an increase in potential in both organs. This means that the outstanding difference in potential between brain and liver might be an additive result of the two potentials existing in both the brain and the liver. Of course, oxidation in both organs would supply the energy necessary for the establishment of a voltage in each case.

It is a further experimental fact that the blood stream surrounding the cells of the liver contains bile, and if the bile fails, death ensues. This might indicate that a major portion of the outstanding potential between the two organs exists in the liver. However, a greater amount of oxidation in the brain would indicate that the major portion of the outstanding potential is developed in the brain. It is not easy to see how either organ as a whole obtains a potential, since the nuclei of the separate cells are not connected so as to be analogous to one large plate of a battery. On the other hand, it is easy to see how the outer portions of each cell could be in contact, and thereby form one big plate of a battery. In any event, however, the greater number of discrete cells in which individually there is potential would mean not an increased potential with increased number of cells, but rather an increased availability of energy. This picture of the battery in the body is similar to the picture of the action present in the battery invented by Daniell, sometimes called in one of its forms the "crow foot battery." In this battery a zinc bar is placed in zinc sulphate contained in a porous cup. The porous cup and its contents are then placed in a copper sulphate solution, into which a copper plate is also placed. The two solutions are kept separate by use of this porous earthenware cup. In the internal circuit of this battery, if one travels from the zinc plate to the copper plate, one finds a rise in potential

of about 0.5 as one passes from zinc to zinc sulphate, and later a second rise in potential as one passes from copper sulphate to copper plate, giving an outstanding voltage of 1.1 volts. To compare the battery in the body to the Daniell cell seems a more valid comparison than comparing it to a common battery of zinc and copper in a sulphuric acid solution, where the entire rise in potential occurs as one passes from zinc to sulphuric acid, with a copper terminal acting as a means to get in contact with the high potential solution with no change in potential occurring at the interface of solution and copper.

The experimental evidence that the hydrogen ion concentration differs in the nuclear part of the cells of both brain and liver from that of the outer portion, together with the fact that oxidation supplies energy in both organs, indicates fairly definitely that there could exist a potential difference between the two portions of the cell itself. These two discrete potential differences existing in the two organs could very well add to give an outstanding potential between the brain and liver with the blood stream between the two organs serving as the connecting medium for that part of the battery commonly called the internal circuit. As stated above, the magnitude of these two distinct voltages would undoubtedly be different, and from two different points of view one could argue that the major portion of the voltage exists in one of the organs. In any event, just what the actual relative magnitudes of these potentials might be, it is not easy to surmise.

It is an experimental fact that the nerve sheath is a very poor electrical conductor, while the nerve core is a good conductor. This would make it very possible for the network of nerves along which electrical impulses are passing to be imbedded within the battery structure itself, and thereby function completely as an electrical circuit. This would mean that the internal and external circuits would be inter-twined in contrast to the usual picture of an electrical circuit where the external circuit is well removed on the outside of the battery structure itself. The returning blood stream from the muscle back to the liver, thence to the heart, could be pictured as a possible return path for the discrete electrical charges sent out by the brain to the individual muscles and organs, and finally to the point of low potential, namely the liver. To recapitulate, electrical impulses must be supplied to the organs and muscles of the body in order that a living organism be maintained. This necessitates a supply of electrical energy which in turn means a transformation of chemical energy, in this case oxidation, into electrical potential, which is one of the two factors involved in elec-

trical energy, the other being quantity of electricity, which for sake of easy understanding we will call current, measured in amperes. Hence the availability of energy supply to the organs and muscles, or rather the energy supply available for the trigger action fed by the nerve impulse is dependent upon a potential and a conducting path existing between brain and liver, both for the internal and the external circuit. On the one hand, if the potential between these organs is lowered, it means that the amount of available energy output is lowered, provided, of course, the electrical resistance is kept constant. Now it has been shown that the electrical resistance of these two organs changes with fatigue and shock, that is, the conductivity is changed. This change of resistance would mean a possible change in energy supply output, even if the potential were not changed.

So from two points of view there could be less energy available on account of the brain and liver changing in their structure incident to fatigue and shock. Experimentally it has been shown that the cell structure in these organs breaks down from fatigue and shock, which would mean a lowering of the potential existent in the cell. Therefore, since the voltage has been decreased, the available energy output would also be decreased. Electrically one must have *low* internal resistance in order that a battery be given a chance to change its chemical potential energy to electrical energy within the internal structure of the battery, and finally transformed into heat, light or mechanical energy in the external circuit. An analogy is here presented in an old so-called dry battery. With age the internal resistance of a dry battery increases, so that one says it is dead. Fundamentally, the energy is still available, that is, the chemical energy in terms of the zinc plate is still available, but it cannot be made an energy output on account of the high internal resistance, so we say it is no good, it is dead.

If, therefore, there is an outstanding decrease in electrical conductivity in the two organs concerned, and also a lowering of potential due to a breaking down of cellular structure, both of these factors would contribute to the diminution in available electrical energy output. It is therefore definitely possible that reduced vitality incident to fatigue and shock might result not only from a lowering of electrical potential, but also from an increase in internal resistance of the body battery. In terms of an equation, one may visualize the above points.

$$\text{Electrical Energy} = \text{Voltage} \times \text{Current}$$
$$EE = V \times C$$

A diminution in either factor, provided the other factor is constant, or a diminution in both factors simultaneously means less energy output. I believe, Dr. Crile, that this picture of conductivity within the body battery and its decrease is an additional point in which you will be interested.

It is an experimental fact that lack of sleep produces death. This could result, as has been previously explained, by the possible decreasing potential or decrease in electrical conductivity. On the contrary, sleep restores the body, and is necessary in normal living. The amount of oxidation taking place in sleep is but fifty per cent of that while awake. As previously discussed, the cell structure in the organs concerned has been shown experimentally gradually to disintegrate, with the possible lowering of electrical potential and change in electrical conductivity, which means a decrease in the possibility of energy output. In sleep, the energy supply for muscular work is practically zero, so that very possibly a major portion of the oxidation which does take place could be very well utilized to build up the potential, which in turn means build up the available energy output for the trigger action previously discussed. To repeat, sleep is necessary for life, and it is therefore very possible from the above argument that during sleep nerve impulse energy is made available by the building up of electrical potential.

The above analogies and visualizations of body action seem to me to be a very plausible argument when considered from a purely physical and energy basis.

APPENDIX C

Experimental Data

APPENDIX C

EXPERIMENTAL DATA

THE ELECTRICAL CONDUCTIVITY OF ANIMAL TISSUES UNDER NORMAL AND PATHOLOGICAL CONDITIONS

By George W. Crile, Helen R. Hosmer and Amy F. Rowland

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The researches of Lillie,[1] Loeb,[2] Osterhout,[3] Mathews,[4] McClendon,[5] Hill,[6] Lucas,[7] and of many other biophysicists and chemists [8] indicate that the functions of the cells of living organisms are related to electrical processes; that the living cell, whether it exists alone or as an element in a complex organism, possesses a certain store of potential energy which is manifested by variations in polarity and by action currents; that variations in the permeability of the living cell to the electrically charged elements of the fluid which surrounds it parallel variations in irritability in response to stimulation; that factors which suspend or abolish irritability also suspend or abolish alterations in permeability.

Every activity of living tissue is accompanied by electrical currents; and many activities are also initiated by electrical currents. In fact, the work of the investigators referred to above shows how strong is the tendency to consider that vital processes depend upon electric energy, by means of which also the protoplasm is renewed, and the whole mechanism is constructed.

In view of this trend of physiological conceptions, the electrical properties of living protoplasm become of vital interest. As this interest extends, the need of definite quantitative data increases. The laws which govern the action of electrical forces in inorganic systems are known exactly. It is possible to calculate exactly how much heat, or what chemical change, or how much work will result from the passage of a current of known strength through a known resistance during a definite period of time.

The two independent factors, current and resistance respectively, depend upon the amount of available electrical energy and the constitution of the system in which its conversion into heat, or chemical change, or other type of work is to be accomplished.

The action of electrical energy in protoplasm, although all the conditions are far more complicated than in inorganic substances, is governed by the same laws. In protoplasm, as in inorganic matter, electrical currents will always choose the path over the lowest available resistance; and in protoplasm, as in inorganic matter, the current pays toll to the friction offered by the system through which it passes.

The facts already established regarding bio-electric currents are sufficient to indicate the importance of further investigation, especially along certain lines. For example: What is the range of the electric conductance of living tissue? How does that range compare with that of other electrical conductors? Is the range of conductance the same for all types of tissue, and in each tissue does it remain constant under all conditions? Is the electric conductance of each tissue a factor in the production of the activities of the organism, to which a fairly constant value can be assigned?

These are questions which occur at once to the most casual student of bio-electric problems, and the fact that the literature offers no clear answer is sufficient reason for a detached study of this subject.

During recent years various investigators have applied measurements of electrical conductivity to the determination of variations in the permeability of protoplasm under varying conditions. In particular the work of Osterhout, Lillie and Loeb along these lines is too well known to be more than mentioned here.

Other investigators have used conductivity measurements as a means for estimating the volume of the corpuscles in blood, for determining the H-ion concentration in body fluids, for measuring the variations in the conductivity of muscle which result from contraction. But none of these investigators has attempted to determine the specific conductance of any tissue.

Early in this century Galeotti [9] carried out a limited number of experiments for the purpose of studying the changes which occur at death. He utilized the tissues of dogs, rabbits, guinea pigs, frogs and turtles, making measurements at successive intervals after the removal of the tissue from the animal. In general, he observed a rapid decrease in conductivity during the first few minutes, followed by a more gradual decrease, which in some instances lasted for several hours. After reaching the minimum,

which he considered marked the death point of the tissue, the conductivity began to rise, gradually at first, and then very rapidly until a very high value was reached.

His values for the normal conductivity of certain rabbit tissues may be of interest as compared with those observed in the work to be described later (Tables 1 and 2).

TABLE 1

Specific conductivity of certain rabbit tissues as determined by Galeotti. (Expressed in reciprocal ohms)

TEMPERATURE	LIVER	HEART	MUSCLE	
			Longitudinal	Transverse
12° C.			00182	00058
18° C.	000268	000799		000804
	00090			
	00053			
24° C.	000269			000789

TABLE 2

Comparison of the specific conductivity of rabbit blood before and after coagulation as determined by Galeotti. (Expressed in reciprocal ohms)

TEMPERATURE	BEFORE COAGULATION	AFTER COAGULATION
38° C.	00569	00566
	00679	00674
	00773	00771
	00539	00526
	00631	00590

For the most part Galeotti worked with the firmer tissues, sections of which he introduced directly between platinum electrodes which were clamped in place after the application of a greater or less degree of pressure. He used only a few animals of each species and does not state that he measured more than one sample of each tissue from any one animal.

The work to be described below was the direct outcome of preliminary measurements made by G. B. Obear of the Case School of Applied Science in the fall of 1917. In spite of inadequate apparatus and a limited number of observations, Doctor Obear's results indicated such consistent relative values of the specific conductivities of certain tissues, especially the cerebrum and cere-

bellum, as to encourage a further research under better conditions. In the fall of 1918, therefore, the research was continued.

Apparatus. The apparatus employed in this research includes that devised by Dr. E. W. Washburn and developed for the market by Leeds and Northrup. It consists of the typical Wheatstone bridge made up of a Kohlrausch slide wire and a resistance box of Curtis coils, with a telephone connected across the ends of the slide wire. Suitable capacities for tuning the circuit and for balancing the capacity of the conductivity cell were inserted in the current. A high frequency (1000 cycles) alternating current was obtained from a constant speed high frequency generator located in another room. All measurements were made with the cell partially immersed in a constant temperature bath. A Freas bath of 300 liters capacity was used, supplemented by a specially constructed cover to minimize fluctuations of temperature, to maintain a sufficiently humid atmosphere, and to insure maintenance of the leads and upper part of the conductivity cell at a uniform temperature.

On account of faulty construction of the glass parts, the automatic temperature regulator for this bath has never worked satisfactorily, but by hand regulation of the lights it has not been difficult to keep the temperature constant within 0.1° C.

Washburn's recommendations in regard to magnetic shielding, grounding, etc., have been carefully observed.

Electrodes. As the early part of this work was done at a time when it was a patriotic duty to conserve platinum, in the preliminary experiments all types of tissue were measured in the same set of electrodes, though it is obvious that this is far from an ideal mode of procedure.

Sections of each tissue were packed into small glass tubes of various sizes, each of which was accurately ground to insure uniform dimensions throughout. The tubes were packed with a sufficient excess of material to procure a slight projection from each end, and were placed between thin platinum electrodes, reinforced by brass backings. Sufficient pressure was applied to bring the electrodes flush with the ends of the tubes, when the electrodes were firmly clamped into place. Great pains were taken to avoid air spaces within the tubes and to insure uniform contact of the tissues with the electrodes. This was not difficult with the softer tissues, such as brain and liver, but with tougher tissues such as muscle and thyroid it was impossible to exclude considerable error from imperfect contact and other variations. The effect of these faults is plainly evident in the greater variation in the conductance values obtained for the latter tissues.

The tubes used for the measurement of the conductivity of the brain, the liver and voluntary and involuntary muscle, were approximately 5 mm. in diameter and 5 mm. in length, while those used in the measurement of the adrenals and the thyroid were of the same length with a diameter of approximately 2.5 mm. Special hard rubber containers were devised for the spinal cord.

The conductance capacities or cell constants of these tubes were determined by repeated measurements of their conductance when filled with 0.01 NKCl, at the same temperature as that used for the tissue measurements.

In the later work larger tubes 1 cm. long $\times$ 1 cm. in diameter were used. These were only partially filled with tissue, and an upper electrode 1 cm. in diameter and pierced by slits was used. The tube was partially filled with closely packed material, and carefully placed in position on the lower electrode, after which the upper electrode was inserted within the tube and carried down until contact was made with the upper surface of the tissue, care being taken, however, to avoid sufficient pressure to cause the extrusion of material through the slits. This upper electrode was then clamped in place and the distance between the two electrodes was accurately measured and recorded.

Every precaution was taken to avoid any undue pressure with the consequent reduction of the fluid content of the tissue and resultant lowering of the conductance, although this danger was lessened by the use of the pierced electrode. Various measurements of different types of tissue were made to determine the effect of varying the pressure, the results of which are illustrated by the groups of measurements shown in Table 3. In each case the successive measurements were made upon the same sample of tissue, the distance between the electrodes, and consequently the pressure, being changed between each two measurements. The results indicate that a greater error is to be feared from the application of too much pressure than from too light a contact.

The cell constants for the tubes used in the later experiments, as for those used in the earlier series, were determined by measurements with 0.01 NKCl with the electrodes at different distances apart, these results being plotted for convenient use in estimating the value of the tissue measurements.

The electrodes were carefully cleansed after each measurement and were replatinized at intervals with a very light coating of platinum black. The electrodes and holders were always placed in the bath long enough before use to insure the thorough warming up of the metal and glass parts, and during the insertion of tissue

were exposed as little as possible to lower temperatures, and even then they were given an opportunity to reach the bath temperature

TABLE 3

Effect of variations in pressure upon the electrical conductivity of animal tissues

TISSUE	DISTANCE BETWEEN ELECTRODES	CONDUCTIVITY (EXPRESSED IN RECIPROCAL OHMS)
	cm.	
Cerebellum		
Section 1	0.78	00133
	0.66	00129
	0.48	00114
Section 2	0.92	00148
	0.55	00128
Section 3	0.60	00140
	0.52	00136
	0.40	00123
Section 4	0.65	00115
	0.50	00108
	0.40	00105
Section 5	0.75	00121
	0.65	00116
	0.50	00116
Section 6	1.11	00158
	0.96	00151
	0.65	00128
Cerebrum		
Section 1	1.24	00183
	0.94	00167
	0.72	00159
Section 2	1.20	00183
	0.92	00170
	0.81	00169
Section 3	1.03	00172
	0.85	00164
	0.64	00145

before measurements were made. It was possible to exercise these precautions with but little loss of time by using two sets of elec-

trodes and holders. All measurements were either made at 39° C. or were corrected to that value from temperatures not over a degree removed from it.

Special points in technic. The object of this investigation being to determine the electric conductivity of animal tissues under conditions as nearly as possible identical with those existing in the living animal, every effort was made to keep the sections of each tissue always at a normal body temperature; to avoid any loss of moisture; and to measure each at the earliest possible moment after

TABLE 4

Conductivity measurements made at varying periods after death to determine onset of post-mortem changes

(Conductivity expressed in reciprocal ohms)

	PERIOD AFTER DEATH							
	Immediate	½ hour	1 hour	1½ hours	2 hours	2½ hours	3 hours	4 hours
Cerebellum	00139	00140	00140	00148	00156	00178	00219	
Cerebrum	00175	00174	00178	00195	00201		00245	
Cerebrum	00181	00180	00185	00192	00202	00224	00241	
Liver	00075	00089	00099	00112	00117	00132	00156	00282
Liver	00081	00094	00097	00121	00165	00187	00236	
After ¼ hour	00082							
Voluntary muscle	00486	00472	00484	00499	00498			00617 *
Voluntary muscle	00194							00210 *

* Following day.

the death of the animal and the removal of the tissue from the body.

A series of measurements was made to determine the onset of post-mortem changes in the different tissues as evidenced by changes in the electric conductivity.

We found that the conductivity of all tissues remained practically unchanged during the first hour after removal from the body; i.e., provided the section had been kept at a constant temperature in a humid atmosphere. The earliest post-mortem changes in conductivity were found in the liver and the brain; the latest in voluntary muscle. No significant change was noted in the brain in less than one hour after removal. In two instances liver changes began in approximately one-half hour after the death of the animal (Table 4). The observation of these changes led to the

adoption of an unvarying routine, in which the liver was always the first tissue to be removed, sectioned and measured.

As a corollary to the measurements made specifically for the purpose of determining the onset of post-mortem changes it may be pertinent to note here that observations of the electric conductivity of the liver after it had been tied off for four hours, but left *in situ,* to produce an effectual hepatectomy, showed the conductivity was increased far above that observed in any experiment in which immediate measurements of the conductivity of the liver were made.

Post-mortem change was not the only factor to be considered, however. It is obvious that animal tissues present no such ideally uniform material as is ordinarily subjected to conductivity measurements. Even if it were possible to secure sections of exact uniformity throughout, completely filling the space between the electrodes, an ideal that thus far has not been satisfactorily attained, it would still be necessary to consider variations in the structure of different parts of the same organ, as well as variations between individual animals.

It was obvious at once that at best we could expect only to establish the limits of variations for each tissue, and that if the results of these measurements were to be of any general physiological value, they must represent the findings in a large number of individuals.

For all these reasons it seemed inadvisable to employ any technic which would delay the prompt measurement of sections after their removal from the animal; or would prevent the examination of a large number of animals, even though such a technic might markedly increase the precision of any single measurement. The precision of a single measurement is of little significance if it is obtained after such a lapse of time as to permit a change from the conditions in the living animal. Also if the normal variation in the conductivity of the same tissue in different animals is several per cent, as one would expect to be the case, it becomes important to multiply the *number of normal measurements* as well as to try for a high degree of precision in single measurements.

On the other hand the absolute maintenance of constancy of method is imperative and no effort has been spared to insure this requisite. Uniformity of technic in the choice of animals, the method of killing, the nature of treatment, the lapse of time and conditions under which the tissue was kept between the killing of the animal and the actual measurement, in the method of meas-

urement and in all other factors has been maintained just as far as possible.

Animals which showed any abnormal condition either before or during treatment or at autopsy were always rejected. The weight and temperature of each animal were recorded. The animals received their last feeding the evening before they were used, as the measurements were always made during the morning; calculations, testing and adjusting of apparatus and so forth being done during the afternoon. The animals were killed by stunning with a blow on the head and the immediate severance of the veins and arteries.

The liver was at once removed, sectioned, packed in warm tubes and placed in the saturated atmosphere of the constant temperature bath for immediate measurement.

In the earlier experiments the block of liver tissue was removed and kept as nearly intact as possible. As it proved difficult to secure sufficient uniformity of filling of the tubes by this method, in the later work the liver substance was separated from the connective tissue and the resultant soft mass was carefully transferred to the tubes. Histologic examination shows that this treatment separates the lobules from the connective tissue, but as the size of the individual liver cell is 5 to 8 microns there is no reason to believe that more than a very small percentage of the liver cells themselves has been destroyed.

The other tissues were removed and sectioned in turn—always in the same order—and measured immediately. The time between the removal of a tissue until its measurement seldom exceeded 20 minutes and under no circumstances was the section allowed to cool perceptibly.

By careful training and close coöperation between principals and assistants, the technic was developed to such a point that it was possible to prepare and measure two sections each from the liver, cerebrum, cerebellum, spinal cord, voluntary muscle and involuntary muscle (heart), and usually one section only from the adrenals and from the thyroid, within 45 minutes after the death of the animal. In the later work, when in the majority of animals measurements were made of only the brain and the liver, it was possible to make measurements of a number of animals each day, and thus secure nearly uniform conditions in the different animals.

At the beginning of the research as many sections as possible were made of each type of tissue until a minimum percentage of variation for each was established.

Thereafter, whenever the measurements of different sections of the same organ failed to agree, the higher value was in general the

TABLE 5

Measurements of the electrical conductivity of normal rabbit tissues

GROUP		CEREBRUM			CEREBELLUM			LIVER			SPINAL FLUID			BLOOD			BILE			HEART			VOLUNTARY MUSCLE			LUNG			SPINAL CORD		
		NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT	NUMBER OF ANIMALS		AVERAGE DEVIATION PER CENT
I.	11/14–11/22/18	7	00186	1.2	7	00155	2.6	9	00075	4.0																		7	00146	5.2
II.	12/14–12/21/18	6	00190	1.4	6	00164	0.8	3	00072	5.9																		6	00180	5.9
III.	2/12– 2/19/19	5	00192	1.6	6	00162	3.3	5	00074	2.2																		4	00116	6.0
IV.	4/21– 5/ 6/19	6	*00138*	*2.0*	5	*00117*	2.0	5	*00086*	*5.0*																		7	*00859*	3.8
V.	5/12– 5/27/19	6	00185	1.5	7	00137	3.6	4	00071	3.0																				
VI.	6/11– 6/18/19	8	00172	1.7	8	00131	1.0	6	00101	1.7																				
VII.	10/1 –10/14/19	13	00177	1.5	11	00134	2.0	11	00097	3.7	4	0194	0.6	5	00852	2.0	4	0152	0.6											
VIII.	10/17–10/27/19	6	00168	1.5	6	00134	3.4	6	00094	4.0	4	0182	3.4	5	00774	2.5	4	0158	2.0											
IX.	11/1 –11/15/19	9	00181	1.3	9	00135	2.2	8	00096	5.0	6	0162	2.0	7	00739	1.3	8	0144	1.8											
X.	11/22–12/ 2/19	4	00179	1.4	5	00128	2.8	5	00061	5.7	3	0184	3.0	4	00772	2.8	4	0139	5.5											
XI.	12/3 –12/10/19	*6*	*00138*	*2.0*	5	*00117*	2.8	8	00091	9.0	5	0187	5.8	7	00746	2.0	7	0164	5.0											
XII.	1/6 – 1/26/20	5	00161	4.5	5	00129	3.2	4	00077	6.5	5	0166	2.4	4	00737	3.2	4	0140	2.6											
XIII.	2/3 – 2/28/20	8	00179	1.9	8	00126	2.3	7	00063	6.3	4	00847	2.2	5	0159	3.9	8	00105	5.1	3	00666	1.6	7	000565 (Range 000507 to 000709)	5.3	5	00167	7.2

one accepted, for the reason that all sources of error under the conditions employed in this work were such as would diminish the conductivity. Thus if the tubes were incompletely filled, that is, if they contained air spaces; if there was imperfect contact with the electrodes; if the material protruded beyond the tubes used in the earlier work, so that the length of the section was greater than that of the containing tube; if too great pressure was exerted; if the temperature of the section was reduced below the normal—any of these conditions would produce a measurement below the true conductivity value.

Two readings of each section were made, an interval of one minute being allowed between the successive readings. The magnitude of the current used was varied according to the resistance of the individual section. The relation of the area of the cross section to the length of the section of each type of tissue was kept within the range that experience showed would give the most favorable minima on the telephone.

Range of electrical conductivity of normal rabbit tissues. The accompanying table (Table 5) gives the average measurements of the electrical conductivity of tissues from 91 normal rabbits. In addition to these measurements preliminary studies made during the development of the technic, bring the total number of normal rabbits studied to over one hundred.

Besides the tissues included in the table, measurements have been made of the thyroid, the adrenals, the kidneys and the spleen. The variation in these measurements was so great that no averages for these tissues have been made and it remains to discover some method by which accurate measurements of these tissues and increased accuracy in the measurement of the spinal cord, of the heart and of voluntary muscle may be secured.

It will be noted that with the exception of the spinal cord, the order of magnitude of the conductivity values of the tissues included in Table 6 never varied.

It was the initial plan to establish a normal range of the conductivity of the various tissues to be used as the basis of comparison for the tissues of all subsequently treated animals. Accident, however, showed the futility of this plan.

During the period in which groups I to III were measured (November, 1918, to February, 1919), the animals had been kept in airy, cool quarters in the country, and provided with an open air run. In April they were removed to a typical animal room which, although well lighted and ventilated, was a great contrast to the former quarters. The effect upon the animals which were

transferred is indicated by the measurements of group IV. The measurements of this group as well as of all treated animals among those that were transferred from the country quarters have been discarded since the great discrepancy between these measurements and those in the earlier as well as in the later groups illustrates most strikingly the effect of variations in environment, season, etc. In this instance the effect of moving and of the changed environment was sufficient to put the animals in the abnormal class, although at autopsy no sign of disease could be discovered. We then began securing animals from a dealer in the country in small groups so that the measurements of all treated animals could

TABLE 6

Range of electrical conductivity of various normal rabbit tissues arranged in the order of magnitude of their conductivity values

Spinal fluid	0.0164 –0.0194
Bile	0.0139 –0.0164
Blood	0.00739–0.00852
Voluntary muscle	0.00580–0.00745
Cerebrum	0.00161–0.00198
Cerebellum	0.00126–0.00151
* Heart	0.00105–0.00117
Liver	0.00061–0.00101
Lung	0.00051–0.00071

* On account of the wide range of the individual measurements of the heart muscle and the fact that in our earliest series its conductivity appeared to be higher, its place in this table may be questioned.

be compared with the measurements of normal animals of the same group.

No conclusions have been drawn from findings in any series unless the difference between the electrical conductivity of the organ in the treated animal and the average measurement of the normal organ in the same group has been greater than the established average deviation of the normal measurements in that group.

It will be noted that throughout these researches, there has been no exception to what appears to be the normal relationship between the cerebrum and the cerebellum in the adult animal; i.e., in every adult animal the conductivity of the cerebrum has been greater than that of the cerebellum. This constant relationship was observed also by Doctor Obear in his preliminary studies. In order to discover whether or not this relation is a characteristic of adult life only, series of fetuses and of young rabbits were measured, and the significant observation was made that in fetuses and imme-

TABLE 7

Relation between the electrical conductivity of the cerebrum and of the cerebellum in fetuses and in young rabbits

	CEREBRUM	CEREBELLUM	LIVER
Mother I	*00163*	*00125*	*00094*
Fetus 1	00087	00125	00049
2	00112	00137	00046
3	00103	00113	
4	00110	00119	00052
5	00070	00136	00048
Mother II	*00185*	*00138*	*00090*
Fetus 1	00097	00099	00033
2	00107		00033
3	00097	00099	
4	00096	00116	00057
Mother III (nearly at term)	*00143*	*00114*	*00099*
Fetus 1	00109	00115	00048
2	00086	00125	00059
3	00104	00119	00037
4	00076	00116	00058
5	00096	00108	00039
6	00092	00094	00045
Approximately 1–2 hours old			
1	00103	00120	00081
2	00096	00131	00088
24 hours old			
1	00122	00114	00072
2	00130	00116	00102
32 hours old			
1	00135	00118	00046
2	00107	00128	00059
4 days old			
1	00111	00140	00092
2	00132	00114	00072
3	00127	00094	00076
6 days old			
1	00145	00140	00078
2	00183		00075
7 days old			
1	00165	00149	00068
2	00156	00162	00066

TABLE 7—*Concluded*

	CEREBRUM	CEREBELLUM	LIVER
10 days old			
1.	00159	00157	00102
2.	00176	00132	00061
1 month, 20 days			
1.	00171	00122	00084
2.	00172	00120	00062
2–3 months			
1.	00188	00158	00118
2.	00195	00147	00099

diately after birth *the conductivity of the cerebellum was higher than that of the cerebrum.* In most of the fetuses measured the conductivity of the cerebellum was as high as in the average adult, while the conductivity of the cerebrum in the fetus and in the newborn rabbits was far below normal. The rise of the conductivity of the cerebrum to the normal level apparently coincides with the emerging of the young rabbit from the nest and the inauguration of its conscious life as an independent individual (Table 7). As will be noted in the table, the conductivity of the liver of the fetus is far below that of the normal adult, but apparently rises to the normal level at birth. It should be noted that on account of the very small size of the fetal cerebellum, it was necessary to use a special electrode and minute glass tubes, so that the possibility of error in the measurements of the cerebellum was greater than in the case of the cerebrum.

An interesting corollary to these observations in rabbits may be noted here. Permission was granted for securing sections of the brains of two patients who died in the hospital on the same day. One died from carcinoma of the stomach and had been conscious until death; the other had been unconscious for days before his death, which was caused by a brain tumor.

As is shown by Table 8, in the patient conscious until death, the conductivities of the cerebrum and the cerebellum while low, undoubtedly as the result of the exhaustion of prolonged disease, nevertheless preserved the relationship observed in all our adult animals; viz., the conductivity of the cerebrum was higher than that of the cerebellum. In the patient who had been unconscious, this relationship was reversed, the conductivity of the cerebellum being higher than that of the cerebrum. It will be noted also that

in this case the value of the conductivity of the cerebellum is very high.

A number of measurements have been made to determine whether or not there is a regional variation in the conductivity of the cere-

TABLE 8

Comparison between the relative conductivities of the cerebrum and of the cerebellum of each of two patients—one conscious until death and one unconscious for days before death

	CEREBRUM	CEREBELLUM
I. Patient conscious until death		
Section I	00143	00116
Section II	00120	00116
Section III	00136	00107
II. Patient unconscious for days before death		
Section I	00139	00181
Section II	00135	00157
Section III	00134	00175

brum. While these preliminary studies are suggestive, the only result which seems sufficiently established to be noted here is the relation between the conductivities of the gray and of the white matter. As shown by Table 9, in every measurement thus far made,

TABLE 9

Relation between the electrical conductivity of the gray matter and of the white matter of the cerebrum

SECTION	GRAY MATTER	WHITE MATTER
1	00213	00117
2	00218	00106
3	00209	00115
4	00227	00147
5	00215	00133
6	00271	00164
7	00202	00139
8	00232	00115
9	00260	00150
10	00240	00143

the conductivity of the gray matter has been markedly higher than that of the white matter.

EFFECTS OF EXHAUSTION DUE TO VARYING CAUSES UPON THE ELECTRICAL CONDUCTIVITY OF THE BRAIN AND THE LIVER. In selecting the types of exhaustion to be included in this research,

we were guided by previous researches in order that we might discover whether or not any measurable relation could be established between the histological changes observed in exhaustion, in particular those in the brain, and the electrical conductivity. That this correlation might be fairly made, we have been constantly guided by the data of the previous researches in the treatment of the animals, dosage, protraction of stimulation, etc.

I. Insomnia. Thirteen Belgian hares of weights varying from 1.414 to 2.588 kgm. were kept awake continuously for 96 hours. During this time they were confined in a large airy room and were given abundant food and water. The animals were kept awake by constant but gentle prodding; they were not hurt in any way, nor at any time did they manifest any discomfort beyond their attempts to settle into corners where they might be left alone. Most of the animals ate and drank freely throughout the insomnia period. Table 10 gives the weight and temperature of each at the beginning and at the end of the period of insomnia.

TABLE 10

Effect of prolonged insomnia—96 hours—upon the weight and temperature of rabbits

RABBIT	INITIAL WEIGHT	FINAL WEIGHT	INITIAL	FINAL
	gm.	*gm.*	*temp.*	*temp.*
I	2.588	2.595	39.6	40.2
II	2.206	1.605	39.0	38.8
III	2.283	2.400	39.6	40.0
IV	2.243	2.254	39.0	39.0
V	2.158	2.215	39.6	39.6
VI	2.343	2.421	39.6	39.6
VII	2.223	2.321	39.6	39.2
VIII	1.730	1.715	39.0	40.0
IX	1.828	2.003	39.2	39.0
X	1.716	1.778	39.0	39.0
XI	1.793	1.630	39.2	39.0
XII	1.414	1.473	38.8	41.0
XIII	2.348	2.328	39.8	39.6

At the end of the insomnia period four of the rabbits were killed at once and conductivity measurements made. Four were put into a darkened room and left undisturbed for 6 hours, when they in turn were killed and conductivity measurements made. The remaining four were kept undisturbed for from 7 to 14 days.

The average conductivities of the cerebrum, cerebellum and liver in each of these groups are shown in Table 11.

TABLE 11

Effect of insomnia and of insomnia followed by periods of rest on the electrical conductivity of the brain and the liver

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
12/14–12/21/18	*Normal II*	*6*	*00189*	*1.4*		*6*	*00164*	*0.8*		*6*	*00072*	*5.9*	
a	Insomnia	4	00184	1.2	— 2.6	4	00154	4.8	— 6.09	5	00075	5.8	+ 4.1
b	Insomnia + 6 hours rest	5	00186	1.5	— 1.5	5	00140	3.1	— 14.6	5	00077	3.6	+ 6.9
c	Insomnia + 1–2 weeks rest	4	00203	4.0	+ 7.4	4	00155	3.0	— 5.4	4	00089	3.9	+ 23.6

II. Fright and exertion. Each of six rabbits was frightened until exhausted by a dog which kept them in a state of intense nervous excitement by barking and thwarted attacks until they were prostrated by the resultant exhaustion. The effect upon the conductivity of the brain and the liver is shown in Table 12 (a).

III. Adrenalin—repeated doses. Repeated doses—2 to 3—of 1-1000 adrenalin (P. D. & Co.) were given to each of 8 rabbits at intervals of from 10 to 20 minutes according to the degree of reaction. The average dose—intravenous—was 0.4 cc. per kgm.; to two rabbits twice this dose was given intramuscularly. Typical changes in pulse and respiration were produced in each animal with ultimate prostration. The conductivity changes are shown in Table 12 (e).

IV. Surgical shock. Each of six rabbits was subjected, under ether, to severe trauma of the intestines and abdominal walls for periods of from 30 to 45 minutes. The resultant conductivity changes are shown in Table 12 (c).

V. Prolonged ether and prolonged nitrous oxid anesthesia. Six rabbits were subjected to 4 hours' continuous ether anesthesia; and six to continuous nitrous oxid anesthesia of the same duration with resultant conductivity changes which are shown in Table 12 (h) and (i).

VI. Thyroid feeding. Six rabbits in fine general condition and of approximately equal weight were each given 5 grains of thyroid extract daily for 3 weeks. All but one showed at first a loss of appetite, with a later increased appetite but a continued loss of weight. With the exception of the one referred to above, which seemed to thrive, the fur of all became rough and coarse in appearance and was shed abundantly; they became nervous and excitable; the eyes were staring in appearance; the skin felt hot to the touch although the clinical thermometer showed no change in temperature. In brief, the animals manifested the typical signs of thyroid intoxication. The probable reason for the exception of the one rabbit noted above appeared at autopsy, which showed a minute and pale thyroid gland as compared with enlarged vascular glands in each of the others.

The losses of weight in each animal were as follows: 18 per cent, 29 per cent, 15 per cent, 36.6 per cent, with a loss of but 4.5 per cent in the exceptional one. One animal died after 2 weeks, with a loss in weight of 33.8 per cent. At the termination of 3 weeks the animals were killed and conductivity measurements made (Table 12 (f)). It should be noted that in this group the thyroid

TABLE 12

Effects of exhaustion from various causes upon the electrical conductivity of the brain and the liver

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
12/14–12/21/18	*Normal II*	*6*	*00189*	*1.4*		*6*	*00164*	*0.8*		*6*	*00072*	*5.9*	
12/ 5–12/14/18	Fright (a)	6	00180	3	— 4.7	6	00152	1.3	— 7.3	6	00118	8	+ 63.8
11/26–12/10/18	Insomnia (b)	4	00184	1.2	— 2.6	4	00154	4.8	— 6.09	4	00075	5.8	+ 4.1
1/ 3– 2/19/19	*Normal III*	*5*	*00192*	*1.6*		*5*	*00162*	*5.3*		*5*	*00074*	*2.2*	
1/ 8– 1/10/19	Surgical shock (c)	5	00168	2.4	— 12.5	5	00154	1.7	— 4.9	6	00091	5.5	+ 22.9
12/ 8–12/18/19	Diphtheria toxin (d)	5	00179	2.7	— 6.7	6	00156	3.1	— 3.7	4	00069	3	— 6.7
1/ 3– 1/ 7/19	Adrenalin injection (e)	8	00184	2	— 4.1	7	00154	1.4	— 4.9	7	00094	3.4	+ 27.02
1/27– 2/17/19	Thyroid feeding (f)	5	00175	2.5	— 8.8	5	00144	3.6	— 11.1	5	00074	4.4	0
1/31– 2/ 8/19	Hydrochloric acid (g)	9	00168	2.7	— 12.5	9	00144	2.7	— 11.1	9	00093	4	+ 25.6
1/30– 2/13/19	Ether—4 hours continuous (h)	6	00177	1.6	— 7.8	6	00130	2.6	— 19.7	6	00097	5.7	+ 31.08
2/13– 2/19/19	Nitrous oxid — 4 hours continuous (i)	6	00184	3.4	— 4.1	5	00139	2.3	— 14.1	6	00094	7	+ 27.02
5/12– 5/27/19	*Normal V*	*6*	*00185*	*1.5*		*7*	*00137*	*3*		*4*	*00071*	*3*	
5/14– 5/26/19	Strychnin (j)	5	00146	3.9	— 21.08	4	00130	5.4	— 5.1	5	00092	3.3	+ 29.5

feeding was protracted until the stage of exhaustion had been reached. Earlier effects are described in a later section.

VII. Hydrochloric acid. In each of four rabbits 1 cc. of hydrochloric acid—10 per cent—was injected in the femoral vein. Each showed an immediate reaction registered in circulatory and respiratory changes, convulsive movements and prostration. The animals were killed in from four to twelve minutes after the injection and conductivity measurements made (Table 12 (g)).

VIII. Strychnin. On account of the wide variation in the response of individual rabbits to strychnin, in this series in which it was desired to produce a massive effect the dosage varied from the just tetanic (0.155 mgm. per kgm. intravenous, Sollman) to the just fatal (0.36 mgm. per kgm. intravenous, Sollman), the dose being repeated if required to produce sufficient reaction. Five animals were included in the series. In each a reaction varying from a general tremor to severe convulsions was produced.

While on account of the variation in dosage and clinical results this is not considered a satisfactory series, the contrast in the conductivity findings to those in a subsequent series in which the incipient effects were noted, is so marked that the series has been included (Table 12 (j)).

Summary. A study of Table 12 shows that in each type of exhaustion there included the conductivity of the cerebrum and of the cerebellum was diminished and the conductivity of the liver was increased except in exhaustion due to thyroid feeding in which case the average conductivity of the liver was unchanged from the normal. With the exception of exhaustion produced by adrenalin injection and by prolonged nitrous oxid anesthesia, in every instance the average conductivity of the cerebrum in exhaustion fell below the lowest individual normal measurement included in the normal group with which comparison is made. If one allows for the average deviation of the cerebellum and of the liver in both the exhausted and the normal animal, in certain instances the apparent change in exhaustion falls within those limits, nevertheless the marked downward tendency in the cerebrum and the cerebellum, and the upward tendency in the liver are obvious.

Incipient effects of exhaustion-producing agents on the electrical conductivity of the brain and the liver. Previous researches and clinical observations had indicated the presence of an incipient stage of shock marked by hyperchromatism of the brain cells as compared with hypochromatism after shock had become established. To determine whether or not a corresponding

TABLE 13

Incipient effects of various exhaustion producing agents upon the electrical conductivity of the brain and the liver

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
6/11–6/18/19	*Normal VI*	*8*	*00172*	*1.7*		*8*	*00131*	*1*		*6*	*00101*	*1.7*	
6/ 9/19	(a) Surgical shock 1 min.	5	00189	1.0	+ 9.8	6	00138	1.3	+ 5.3	4	00108	1.9	+ 6.9
6/ 6/19	5 min.	3	00175	0.8	+ 1.7	3	00142	1.9	+ 8.3	3	00116	6.5	+ 14.8
6/10/19	(b) Ether—stage of excitement	3	00195	0.6	+ 13.3	3	00126	2.3	— 3.8	2	00119	4.2	+ 17.8
6/11/19	(c) Nitrous oxid—stage of excitement	3	00174	1.6	+ 1.1	3	00139	6.3	+ 6.1	3	00099	6.6	— 1.9
6/12–6/16/19	(d) Strychnin	4	00193	3.0	+ 12.2	4	00143	2.1	+ 9.1	3	00092	7.3	— 8.9
6/13–6/16/19	(e) Adrenalin	4	00181	3.4	+ 5.2	4	00129	2.7	— 1.5	4	00095	4.6	— 5.9

early increase in the electric conductivity of the brain precedes the ultimate decreased conductivity after the state of exhaustion or shock is established, a number of studies of the incipient effects of some of the shock-producing agents noted above was made.

I. Incipient effects of intense trauma. Under light ether anesthesia two groups of rabbits were subjected to extreme shock-producing manipulations for periods of 1 and of 5 minutes respectively. They were killed immediately and electric conductivity measurements made (Table 13 (a)).

Incipient effects of strychnin. Each of five rabbits was given a fatal dose (0.36 mgm. per kgm.) intravenously and killed 1 minute after the injection (Table 13 (d)).

Incipient effects of adrenalin. Each of three rabbits was given an intravenous injection of 0.4 cc. per kg. of 1-1000 adrenalin (P. D. & Co.) and killed 1 minute later (Table 13 (e)).

Incipient effects of ether and of nitrous oxid anesthesia. To one of two groups of rabbits ether was administered for from 2 to 5 minutes; nitrous oxid being administered to the other group for like periods. Each animal was killed just at the termination of the first stage of anesthesia—the stage of excitement (Table 13 (b and c)).

Diphtheria toxin. To various groups of rabbits twice the lethal dose of diphtheria toxin (P. D. & Co.) was given intravenously, the animals being killed at intervals varying from 5 minutes to 1 hour after the dose was received. The progressive effects are shown in Table 14.

Summary. With every exhaustion-producing agent studied, the initial effect was an increased conductivity of the cerebrum followed by a decrease to below the normal when the stage of exhaustion was reached. The early effect of stimulation upon the cerebellum appeared to vary, but a study of the clinical behavior of the animals, especially of the initiation of the respiratory and circulatory changes, together with an examination of the individual measurements, would seem to indicate that a like unvarying rule exists in the case of the cerebellum, but that the protraction of the incipient stage is shorter than in the case of the cerebrum. Many additional experiments are required to establish this point.

A study of the individual measurements of the liver would appear to indicate an immediate tendency to decrease followed by an increase to above the normal.

The effects of diphtheria toxin in the presence of morphin on the electrical conductivity of the brain and

TABLE 14

Progressive effects of the injection of diphtheria toxin upon the electrical conductivity of the brain

DATE OF EXPERIMENT	PERIOD AFTER INJECTION OF TOXIN	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*
5/12–5/27/19	*Normal V*	*6*	*00185*	*1.5*		*7*	*00137*	*3*	
6/2–6/4/19	15 min.	2	00226	1.9	+ 22.0	3	00137	0.9	0
6/2–6/4/19	30 min.	3	00194	1.3	+ 4.8	3	00128	1.8	— 6.5
5/27–5/29/19	1 hour	3	00180	1.7	— 2.7	3	00109	0.5	— 20.4
12/3/19–1/6/20	*Normal XI*	*7*	*00172*	*2.4*		*8*	*00127*	*2.8*	
12/15/19–1/2/20	15 min.	3	00189	1.2	+ 9.8	3	00154	1.7	+ 21.2
1/7/20	30 min.	2	00174	3.8	+ 4	2	00131	0	+ 3.1
1/3–2/19/19	*Normal III*	*5*	*00192*	*1.6*		*5*	*00162*	*5.3*	
2/8–2/18/19	4 hours	5	00179	2.7	— 6.7	6	00156	3.1	— 3.8

TABLE 15

Comparison of the effects of diphtheria toxin alone and of diphtheria toxin in the presence of morphin on the electrical conductivity of the brain and the liver

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
12/14–12/21/18	*Normal III*	*6*	*00192*	*1.6*		*6*	*00162*	*5.3*		*3*	*00074*	*2.2*	
2/ 8–12/18/19	Diphtheria toxin	5	00179	2.7	— 6.7	6	00156	3.1	— 3.7	4	00069	3.0	— 6.7
2/ 6– 2/13/19	Morphin	6	00185	4.6	— 3.6	6	00148	4.1	— 8.6	6	00065	6.9	— 12.2
2/ 6– 2/18/19	Diphtheria toxin and morphin	6	00187	2.6	— 2.6	6	00164	3.2	+ 1.2	6	00075	4.2	+ 1.4

LIVER. The control of infection by morphin, so strikingly illustrated by the Alonzo Clark treatment of peritonitis, and the comparison of the histologic effects of diphtheria toxin alone and in the presence of morphin, led us to perform a series of experiments to determine whether or not the protective effect of morphin would be manifested by any diminution of the conductivity changes produced by diphtheria toxin alone.

Coincidentally with the series of experiments described above in which the rabbits were killed 4 hours after the intravenous injection of twice the lethal dose of diphtheria toxin, to each of another group 5 grains of morphin were given hypodermically in two doses, 1 hour apart; twice the lethal dose of diphtheria toxin being given intravenously 15 minutes after the second dose of morphin was received. The animals were killed 4 hours after receiving the diphtheria toxin.

To each of a third group morphin alone was administered as above, and the animals killed 4 hours after the second dose. The conductivity measurements are given in Table 15.

EFFECTS OF THYROID FEEDING AND OF IODIN, AND OF ADRENALIN IN THE PRESENCE OF EACH, UPON THE ELECTRIC CONDUCTIVITY OF THE BRAIN AND THE LIVER. In a preceding section we have shown that the late effects of thyroid feeding are identical with the late effects of other exhaustion-producing agents.

Three later series of experiments were performed to discover the earlier effects of thyroid feeding and what, if any, effect upon the conductivity of the brain is produced by adrenalin in the presence of thyroidism, or of iodism.

The results of these series are shown in Tables 16 and 17, in which have been included also for ready comparison the effects of thyroid feeding to the point of exhaustion, and the immediate effect of the injection of adrenalin.

The animals included in Table 16, series II and III, had been given 2 to 3 grains of thyroid extract daily for a period of 4 weeks. It will be noted that while thyroid extract alone increases the conductivity of the cerebrum and of the cerebellum, the injection of adrenalin in the thyroid-fed animals produced a tendency to return toward or below the normal.

In Table 17 the same contrast in the effects of iodoform and of iodoform plus the injection of adrenalin upon the conductivity of the cerebrum and of the cerebellum will be noted; i.e., iodoform alone increases the conductivity of the brain, this effect tending to be neutralized by adrenalin.

TABLE 16

Early and late effects of thyroid feeding and thyroid feeding plus adrenalin upon the electrical conductivity of the brain and the liver

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
Series I													
1/ 3– 2/19/19	*Normal III*	*5*	*00192*	*1.6*		*5*	*00162*	*5.3*		*5*	*00074*	*2.2*	
1/27– 2/17/19	Thyroid feeding, late effects	5	00175	2.5	— 8.8	5	00144	3.6	— 11.1	5	00074	4.4	0
Series II													
12/3/19–1/6/20	*Normal XI*	*7*	*00172*	*2.4*		*8*	*00127*	*2.8*		*8*	*00091*	*9*	
12/ 3–12/ 9/19	Thyroid feeding	3	00189	0.9	+ 9.8	3	00147	0.9	+ 15.7	4	00080	2.5	— 12.08
12/ 3–12/ 5/19	Thyroid feeding plus adrenalin	2	00188	0.3	+ 9.3	3	00127	1.1	0	2	00070	0	— 23.07
Series III													
2/ 3– 2/28/20	*Normal XIII*	*8*	*00179*	*1.9*		*8*	*00126*	*2.3*		*7*	*00063*	*6.3*	
2/17– 2/18/20	Thyroid feeding	2	00199	2.6	+ 11.1	1	00137		+ 8.7	2	00061	4.1	— 3.1
2/17– 2/18/20	Thyroid feeding plus adrenalin	3	00163	2.1	— 8.9	3	00128	2.3	+ 1.6	3	00050	11.3	— 20.6
Early effects of adrenalin alone													
6/11– 6/18/19	*Normal VI*	*8*	*00172*	*1.7*		*8*	*00131*	*1*		*6*	*00101*	*1.7*	
6/13– 6/16/19	Adrenalin	4	00181	3.4	— 33.4	4	00129	2.7	— 1.5	4	00095	4.6	— 5.9

TABLE 17

Effect of iodoform and of iodoform plus adrenalin on the electrical conductivity of the brain and the liver

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
Series I.													
6/11– 6/18/19	*Normal VI*	*8*	*00172*	*1.7*		*8*	*00131*	*1*		*6*	*00101*	*1.7*	
6/17– 6/18/19	Iodoform	3	00193	0.5	+ 12.2	4	00134	1.1	+ 2.2	4	00131	7.3	+ 29.7
Series II.													
2/ 3– 2/28/20	*Normal III*	*8*	*00179*	*1.9*		*8*	*00126*	*2.3*		*7*	*00063*	*6.3*	
2/ 6/20	Iodoform	2	00194	4	+ 8.3	2	00140	4	+ 11.1	2	00064	6.7	+ 1.5
2/ 5/20	Iodoform plus adrenalin	2	00176	2.2	— 1.6	2	00124	0	— 1.5	2	00083	1.2	+ 31.7
Early effects of adrenalin alone													
6/11– 6/18/19	*Normal VI*	*8*	*00172*	*1.7*		*8*	*00131*	*1*		*6*	*00101*	*1.7*	
6/13– 6/16/19	Adrenalin	4	00181	3.4	+ 5.2	4	00129	2.7	— 1.5	4	00095	4.6	— 5.9

TABLE 18

Comparison of the effects of an acid with the effects of an alkali upon the electrical conductivity of the brain and the liver

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
6/11–6/18/19	*Normal VI*	*8*	*00172*	*1.7*		*8*	*00131*	*1.0*		*6*	*00101*	*1.7*	
6/19–6/20/19	Sodium bicarbonate	6	00178	2.2	+ 3.4	6	00139	3.1	+ 6.1	6	00087	6.6	— 13.8
1/ 3–2/19/19	*Normal III*	*5*	*00192*	*1.6*		*5*	*00162*	*5.3*		*5*	*00074*	*2.2*	
1/31–2/ 8/19	Hydrochloric acid	9	00168	2.7	— 12.5	9	00144	2.7	— 11.1	9	00093	4.0	+ 8.1

TABLE 19

Comparison of the effects of magnesium sulphate and of magnesium sulphate plus calcium chloride

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	LIVER	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*				*per cent*
	Normal XIII	*8*	*00179*	*1.9*		*8*	*00126*	*2.3*		*7*	*00063*	*6.3*	
2/ 3–2/28/20	$MgSO_4$	4	00164	1.2	— 8.3	3	00130	2.2	+ 3.1	4	00064	1.7	+ 1.5
2/19–2/27/20	$MgSO_4 + CaCl_2$	4	00171		— 4.4	4	00116	2.1	— 7.9	3	00054	5.8	— 14.2

Each of the animals in the iodoform series had received an intraperitoneal injection of 75 grams of iodoform introduced through a small abdominal opening. The incision was closed and the animals killed on the following day. Each showed febrile phenomena. There was an early rise of temperature of from 0.4 to 1.3° C. which was persistent in all but three of the cases; in those three the temperature dropped to from 0.1 to 1.0° C. below the initial temperature.

That the increased conductivity produced by iodoform cannot be due to the permeation of the tissues by the iodin is shown in series II, Table 17, in which, while the conductivity of the cerebrum and of the cerebellum is markedly increased, the conductivity of the liver is practically unchanged.

An essential corollary to these experiments would be the measurement of the conductivity of the brain in thyroidectomized animals after the injection of iodoform.

OPPOSITE EFFECTS OF ACID AND OF ALKALI INJECTION UPON THE ELECTRICAL CONDUCTIVITY OF THE BRAIN AND THE LIVER. In each of 6 rabbits 10 cc. of a saturated solution of sodium bicarbonate were slowly injected through the marginal ear vein. Each animal was killed 2 hours after the injection and sections taken for conductivity measurements.

As will be seen in Table 18, the injection of sodium bicarbonate increased the conductivity of the brain and decreased the conductivity of the liver, while the injection of hydrochloric acid, as described in a preceding section of this report, decreased the conductivity of the brain and increased the conductivity of the liver.

MISCELLANEOUS GROUP—SHOWING THE EFFECTS OF VARIOUS AGENTS UPON THE ELECTRIC CONDUCTIVITY OF THE BRAIN. In this section are included a number of preliminary studies. No comment is made, as they should be extended before any conclusions can be drawn. The indications are sufficiently shown in Tables 19 and 20.[1]

I. Magnesium sulphate—calcium chloride. To each of four rabbits 6 cc. per kgm. of a 25 per cent solution of magnesium sulphate was given intramuscularly. The animals were killed one-half hour after the anesthesia was complete and sections taken for conductivity measurements.

To each of another group of four rabbits a like dose of magne-

[1] Sollman's *Laboratory Guide in Pharmacology* was used as a guide in determining the dosage in each group of experiments included in this section.

TABLE 20

Effects of various agents upon the electrical conductivity of the brain

DATE OF EXPERIMENT	STIMULUS	NUMBER OF ANIMALS	CEREBRUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL	NUMBER OF ANIMALS	CEREBELLUM	AVERAGE DEVIATION PER CENT	PERCENTILE DEVIATION FROM NORMAL
					per cent				*per cent*
11/ 1–11/15/19	*Normal IX*	*9*	*00181*	*1.3*		*9*	*00135*	*2.2*	
10/28–10/29/19	(a) *Calomel*	3	00166	1.0	— 8.2	3	00136	0.3	+ 0.7
10/29–11/21/19	(b) *Caffein*								
	Single massive dose	4	00163	1.5	— 9.9	4	00142	1.6	+ 5.1
	Repeated doses	4	00177	2.2	— 2.2	4	00141	1.5	+ 4.4
	Repeated doses 2 successive days	5	00158	1.6	— 12.7	5	00142	3.2	+ 5.1
11/22–12/ 2/19	*Normal X*	4	00179	1.4		5	00128	2.4	
11/19–12/ 6/19	(c) *Sodium bromid*								
	After 1 hour	3	00184	1.8	+ 2.7	3	00128	4.1	0
	" 2 hours	3	00180	0.9	+ 0.5	2	00126	0.5	— 1.5
	" 15–16 hours	2	00180	0	+ 0.5	2	00145	1.1	+ 13.2
	" 24 hours	2	00174	4	— 2.7	2	00127	4.6	— 0.7
	" 48 hours	2	00170	1.4	— 5.02	2	00119	0.6	— 7.03
	Normal XII	*5*	*00161*	*4.5*		*5*	*00129*	*3.2*	
1/ 6– 1/26/20	(d) *Cocaine*								
1/15– 1/17/20	Intravenous	4	00167	0.7	+ 3.7	4	00133	1.4	+ 3.1
	Intramuscular	2	00155	2.8	— 3.7	2	00115	1.5	— 10.8

sium sulphate was given, followed, one-half hour after anesthesia was complete, by the intravenous injection of 8 cc. per kgm. of a 3 per cent solution of calcium chlorid. In each case the animal became completely conscious almost immediately after the calcium chlorid injection. It was killed at once and conductivity measurements made.

The contrasting results in the two series are shown in Table 19.

II. Calomel. To each of three rabbits 2 cc. per kgm. of a 0.5 per cent solution of calomel in sodium thiosulphate was given hypodermically. The animals were killed 24 to 30 hours later. Each showed marked diuresis and diarrhea, with some salivation (Table 20 a).

III. Caffein. (a) To each of 5 rabbits 4 cc. per kgm. of a 1 per cent solution of caffein was given intravenously. Each showed extreme toxic effects and died within 10 to 15 minutes.

(b) To each of four rabbits 1 to 2 cc. per kgm. of the 1 per cent caffein solution was given hypodermically in two successive doses about 10 minutes apart, the interval being determined by the clinical effects. These showed less marked but positive clinical effects terminating in milder convulsions. The animals were killed when the convulsions appeared.

(c) To each of five rabbits two or three doses as in the last preceding series were given and the animals kept until the following day, when a final dose was given and the animal killed during the resultant convulsion.

The average effects of the caffein upon the electrical conductivity of the animals in each of these groups is shown in Table 20 b.

IV. Sodium bromid. Twelve rabbits were divided into 5 groups and given sodium bromid (3 gm. per kgm.) through a stomach tube in single or repeated doses, as follows:

Group 1, 3 rabbits, 1 dose—killed 1 hour later.
Group 2, 3 rabbits, 2 doses—1 hour apart—killed 1 hour after last dose.
Group 3, 2 rabbits, 1 dose—killed 15-16 hours later.
Group 4, 2 rabbits, 1 dose on each of two successive days—killed 1 hour after second dose.
Group 5, 2 rabbits, 1 dose on each of 4 successive days—killed 1 hour after last dose.

The average effects upon the electric conductivity of the brains of the animals in each group are shown in Table 20 c.

V. Cocaine. (a) To each of 4 rabbits 1.2 cc. per kgm. of a 5 per cent solution of cocain was injected intravenously. The

injection was followed by a mild convulsion followed by complete relaxation. The animals were killed in from one-half to three-quarters of an hour after the dose was given.

(b) To each of two rabbits 2 cc. per kgm. of a 5 per cent solution of cocain was injected intramuscularly, and the animals killed one hour later (Table 20 d).

Measurements of the electric conductivity of pathological human tissues. In view of the finding of Loeb, Lillie, McClendon and other physical chemists that the permeability of the ovum is increased by fertilization, and the indication of their researches and our own that any alteration in function of the cells is attended by an alteration in their electric conductivity, one would infer that the electric conductivity of tissues in which the cells are in as active a state as in cancerous tissue would be higher than the electric conductivity of normal tissue. We therefore included in our research measurements of the electric conductivity of malignant and benign tumors and of various precancerous conditions.

In this study we have measured 219 sections from 159 clinical cases. These have included malignant and benign tumors of the breast and of the uterus, ulcer and carcinoma of the stomach, carcinoma of the rectum, malignant and benign tumors of the mouth, jaws, and neck, x-ray burns and various types of goiters—hyperplasia, fetal adenoma, multiple adenoma, toxic adenoma, exophthalmic goiter, simple colloid goiter, thyroiditis. Whenever possible adjacent normal tissue has been measured for comparison. The pathological diagnosis and differentiation of different types of tissue in single specimens were made by the pathologist of the surgical section at Lakeside Hospital.

Among the goiters the highest conductivities were found among the adenomata. Variations in conductivity are well illustrated by the following measurements of a goiter, one portion of which was malignant. Three specimens from this gland gave the following measurements: colloid portion, 0.00124; early degeneration, 0.00159; rapidly growing portion, 0.00346.

The highest conductivities were found in the degenerating adenomata and the malignant thyroids; the conductivities of the hyperplastic thyroids were lower; and the conductivities of the colloid goiters were the lowest of any of the pathological tissues studied.

In all instances in which comparative measurements were made the conductivity of the malignant growth was higher than that of

a normal portion of the same organ, as is illustrated by the following examples:

Sarcoma of the uterus:	
Comparatively normal portion	0.00367
Sarcomatous portion	0.00550
Mixed tumor of parotid:	
Comparatively normal gland	0.00153
Malignant portion (2 sections)	0.00922 0.01058
Carcinoma of the breast:	
Comparatively normal portion	0.00225
Carcinomatous portion	0.00581
Carcinoma of the pylorus:	
Normal mucosa	0.00126
Base of growth	0.00469

In the light of these comparisons the following measurements of the conductivities of x-ray burns and of the adjacent normal tissues are significant.

Case I. Normal tissue, 0.00103; x-ray burn, 0.00717.
Case II. Normal tissue, 0.00151; x-ray burn, 0.00366.

The outer growing parts of cancers showed a high conductivity in contrast with the conductivity of the central non-growing parts.

Carcinoma of the thyroid:	
Center of growth	0.00101
Periphery	0.00528
Carcinoma of the uterus:	
Center of growth	0.00493
Periphery	0.00658

SUMMARY AND CONCLUSIONS

1. In an attempt to determine the specific electric conductivity of various normal animal tissues and whether or not variations in function are accompanied by measurable changes in their electric conductivity, 4,764 sections from 455 rabbits and 219 sections of pathological human tissues have been measured.

2. The specific normal conductivity of the cerebrum, cerebellum and liver can be estimated within a narrow range; while the nor-

mal conductivity of other tissues can be estimated within a sufficiently narrow range to determine the order of their relative conductivities.

3. The spinal fluid has the highest conductivity of any of the tissues studied, the lung and the liver the lowest.

4. The order of the conductivities of the following tissues was unchanged in all the animals studied with the exception noted in (6); viz., spinal fluid, bile, blood, voluntary muscle, cerebrum, cerebellum, liver, lung. In a limited number of observations the conductivity of the heart fell between that of the cerebellum and the liver, but on account of the wide range of the individual measurements, this cannot be considered as established.

5. The conductivity of normal tissues appears to vary according to the season and the general environment.

6. In every normal adult animal studied the conductivity of the cerebrum was higher than the conductivity of the cerebellum. In fetuses and in very young rabbits this relation was reversed—the conductivity of the cerebellum being higher than the conductivity of the cerebrum until about the time when the young rabbit left the nest and began voluntary activities, when the normal adult conductivity relation of the cerebrum and the cerebellum appeared to be established. A most significant corollary to this observation was found in the post-mortem examination of the brains of two patients, one of whom died after days of unconsciousness resulting from a brain tumor, while the other who died from carcinoma of the stomach, was conscious to the end. In the patient who had been unconscious, *the conductivity of the cerebellum was higher than that of the cerebrum.* In the other patient, as in all our normal animals, the conductivity of the cerebrum was higher than that of the cerebellum.

7. The conductivity of the gray matter of the brain is higher than that of the white matter.

8. Exhaustion from any cause—surgical shock, insomnia, emotion (fright), infection, etc.—is marked by a *diminished conductivity of the brain* and an increased conductivity of the liver.

9. The immediate effect of activation appears to be an increased conductivity of the brain, tending later to decrease as the stage of exhaustion approaches. This has been shown to be an immediate effect of physical injury; an early effect of the injection of diphtheria toxin; an immediate effect of the injection of adrenalin.

10. Thyroid feeding in large doses over a prolonged period produces the typical symptoms of hyperthyroidism with ultimate

exhaustion accompanied by the changes in the conductivity of the brain typical of exhaustion from any other cause; i.e., the conductivity of the cerebrum and cerebellum is decreased.

11. Thyroid feeding in moderate doses until the symptoms of hyperthyroidism appear but not to the stage of exhaustion produces conductivity changes in the brain typical of the stage of stimulation produced by other agents; i.e., increased conductivity of the brain and decreased conductivity of the liver. These changes were diminished or reversed by the administration of adrenalin.

12. Iodoform increases the conductivity of the brain and of the liver. These changes are reversed by adrenalin.

13. The injection of hydrochloric acid produced *diminished conductivity of the cerebellum and cerebrum and increased conductivity of the liver.* The injection of sodium bicarbonate produced *increased conductivity of the cerebellum and cerebrum and decreased conductivity of the liver.*

14. Rabbits were kept awake continuously for 96 hours. At the end of this period a number were killed and conductivity measurements made; others were allowed a brief period of rest of from four days to a week. At the end of the insomnia period the *conductivity of the brain was decreased* and the conductivity of the liver was increased; at the end of the short period of rest, the conductivity of the brain and of the liver was but little changed, if at all; at the end of the longer periods of rest, the brain was again approaching its normal conductivity.

15. A limited number of observations indicate that the changes produced by infection are minimized provided the infection is applied in the presence of morphin: that is, excessive infection alone decreases the conductivity of the brain and increases the conductivity of the liver; in this limited series of observations the conductivity of the brain remained practically unchanged when diphtheria toxin was administered in a morphinized animal, and the conductivity of the liver was but slightly altered.

16. A limited series of observations of the influence upon the electric conductivity of the brains of animals of various agents, which produce marked clinical effects, indicate that the progress of alteration in function produced by any agent is coincident with changes in electric conductivity.

17. In the pathological specimens studied, active malignant growths had a high conductivity in comparison with adjacent normal tissue and the inactive portions of the same growth, and with growths of a non-malignant type.

GENERAL CONCLUSIONS

1. Influences which affect the general physical condition of the organism produce changes in electric conductivity in the dominating reactive tissues, these changes being uniformly and measurably manifested in the brain and the liver. Apparently these changes in conductivity appear more promptly than any gross clinical alteration.

2. Apparently the liver is more promptly and more markedly affected than any other tissue, as animals showing either no or very slight changes in the cerebrum and cerebellum will often show a marked alteration in the conductivity of the liver. On account of the wide variation in liver measurements and the apparent susceptibility of this organ to seasonal and environmental changes, the effects of applied agents are best determined by measurements of the cerebrum and cerebellum.

3. A study of the individual measurements from which the averages have been computed seems to indicate that the variations represent slightly different stages in a process that varies in rate in different animals and in the different organs of the same animal.

4. In view of the above indication and the direct evidence of the measurements we feel justified in the assumption that the first effect of stimulation within the organism is a slight decrease of the conductivity of the liver followed by a rapid continuous rise to above the normal as the state of exhaustion approaches; a slight and prompt increase in the conductivity of the cerebellum followed by a gradual continuous fall; a relatively slower increase in the conductivity of the cerebrum followed by a gradual continuous decrease.

5. These studies indicate that electric conductivity measurements provide a means whereby to further the interpretation of the normal operation of the organism, and whereby to measure the progress of pathological processes within the various organs and tissues.

6. From our findings to date, it would appear that the *intracellular changes in exhaustion and shock which are revealed by the microscope are paralleled by alterations in electric conductivity, and that both the histologic and the electric changes bear a direct relation to the vitality of the organ.*

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THERMO-ELECTRIC STUDIES OF TEMPERATURE VARIATIONS IN ANIMAL TISSUES

I. General Considerations; Description of Apparatus and Technic

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In previous publications [1, 2] we have demonstrated that the intracellular changes in excitation and exhaustion which in certain organs and tissues—notably the brain—are revealed by the microscope, are manifested also by alterations in electrical conductivity.

Histologic studies and measurements of electrical conductivity must be prosecuted after the death of the animal, although, as noted in a preceding report,[2] with proper precautions it is reasonable to believe that the changes noted at least parallel the progress of processes in the living animal. However, to determine finally whether or not the variations in the histologic picture and in the electric conductivity are parts of one and the same process as that manifested by changes in functional activity, it was necessary to devise some method by which the functional changes in the cells might be measured in the living animal. Only by such a measure could it be ascertained whether or not changes in electric conductivity indicate changes in functional activity. Clinical evidence would appear to demonstrate that this is the case, but clinical evidence cannot be accurately measured, nor does it identify without question the organs which are principally concerned. Some accurate index that could be applied to the organ itself in the living animal was essential.

Variations in functional activity indicate variations in oxidation; variations in oxidation are manifested by variations in heat production. If heat is a constant product of functional activity, then, if we could measure the progressive changes in the temperature of the various tissues and organs during the various phases of excitation and exhaustion under conditions identical with those

formerly studied, we not only should be able to check our findings in the previous researches but should be able finally to link those findings with the clinical evidence.

As the first means to this end we decided to use the method of measurement employed by physicists for the measurement of minute temperature variations, that is, to employ thermocouples so constructed that they could be applied to the brain, liver, muscle or other tissue of the living animal.

This method of measuring variations in the temperature of living tissues was first utilized, as far as we have been able to discover, by Becquerel and Breschet [3] in 1835, when they used thermocouples to determine variations in temperature in different parts of the body in different pathological conditions. They inserted thermocouples into various muscles of the arm, the thigh and the leg, into the abdomen and into different portions of tumorous growths. They even inserted the couples into the auricles of the heart to determine the difference between the temperature of arterial and venous blood. Their reasons for undertaking this research are significant. In their *Premier Memoire sur la Chaleur Animale,* they state in brief that this research was suggested as the result of certain other attempts to answer the following questions: "Are the vital forces of an electrical or chemical nature? Has the organism its own peculiar mode of action?"

In 1869 and 1870 Schiff [4] published the results of an extensive research undertaken in the hope of answering the following questions:

> Is the stimulation of the nerves of sensation necessarily transmitted to the cerebral hemispheres, or is the direct transmission of the stimulation in the normal animal arrested at the spine or in the pons Varolii? Furthermore, is the transmission to the brain in accordance with the fundamental laws governing transmission along the nerves? Is the formation of a perception in the brain accompanied by phenomena which the means of investigation at our command will not permit us to regard as subject to the general laws of material movement?

In Schiff's research thermocouples were employed which were applied directly to exposed nerves or inserted into different parts of the brain. The author felt that he had established the following points:

1. That the irritation of the nerve increased its temperature.
2. That successive irritations produced diminished response of the nerve.

3. That every peripheral irritation gave a response in the brain manifested by increased temperature.

4. That the temperature was always higher in the right hemisphere of the cerebrum.

5. That there was no temperature change in the cerebellum.

6. That no response to peripheral irritation was noted in the brains of animals under morphin. "These preparations (of opium) especially of morphin do not permit any manifestation to an appreciable degree of the effect of sensory irritation on the temperature of the brain."

7. That not only tactile sensation but stimulation of all the organs of special sense produced an increase in the temperature of the cerebrum.

8. That repeated excitation of the special senses—sight, hearing —produced progressively lessening effects as manifested by temperature changes in the brain. "It is seen, consequently, that this last series of experiments is perhaps the most important for our conclusions."

9. That psychic excitation, independent of the sensations which produced it, was accompanied by a production of heat in the nerve centers, which was quantitatively greater than the heat engendered by less complex sensations.

The author believed that his observations definitely excluded the possibility that the temperature changes noted were due to circulatory changes; and that his experiments were sufficient "to establish, with all the desirable precision, that the production of heat which we have observed is really the result of excitation which is peculiar to and an intrinsic part of the nerve elements."

In 1868 Rosetti (5) recorded an attempt to construct thermocouples for the measurement of body temperature and reported one practical application.

Also in 1868, Lombard (6) described a thermopile devised by him for the study of external temperature changes. In particular he studied the relation of heat to mental work as manifested by temperature changes of the outside of the head, which he believed could be referred to changes in the temperature of the brain. Albutt (7) in 1875 employed similar apparatus to that of Lombard in an attempt to discover the relation between internal and external heat.

From that time the literature records the occasional use of thermo-electric apparatus for the measurement of changes in bodily heat, but no especially noteworthy researches are recorded until within recent years. A bibliography of these intermediate studies is offered by Benedict and Snell (8) in their description of a

resistance thermometer devised by them for the observation of variations in the rectal temperature of subjects in a calorimeter chamber.

In 1909 Gamgee (9) devised a clinical apparatus in which thermocouples were employed for the continued measurement and registration of diurnal variations in temperature, and following his lead, Sims, Woodhead and Varrier-Jones (10) produced a thermo-electric apparatus which could be used consecutively for 24 hours or more without disturbing the patient.

In 1911, A. V. Hill (11) utilized the thermo-electric method in an investigation to determine the presence or absence of temperature changes during the transmission of a nervous impulse. He concludes that

"Tetanus, up to 25 secs., of a live nerve, does not cause a change of temperature (other than at the seat of excitation) of more than about $\pm 6 \times 10^{-6}$ ° C. There is no evidence of any change at all, but the method does not allow conclusions beyond this limit. For every single propagated disturbance, the change of temperature, therefore, cannot exceed about 10^{-8} ° C., a hundred millionth of a degree. This corresponds to an oxidative process in which only one molecule of oxygen is used in a space of visible size, viz.,—a 3·7μ cube. This suggests very strongly, though of course it does not finally prove, that the propagated nervous impulse is not a wave of irreversible chemical breakdown, but a reversible change of a purely physical nature."

A thorough search of the literature, however, has discovered no reference to the measurement of variations in the temperature of the brain and other internal organs under diverse conditions with the exception of the work of the investigators cited above, that of Stengel and Hopkins (12) on the intragastric temperature and the work of Macleod and Taylor (13) on the effects of hot and cold applications on the superficial and deep temperatures.

By the invitation of Dr. E. P. Hyde and with the active co-operation of Dr. W. E. Forsythe, our initial experiments were performed at the Nela Research Laboratory. A copper-constantan thermocouple, the wires passed through a glass tube in the end of which the couple was sealed, was used, the "cold" junction being placed in melting ice in a thermos bottle.

Three rabbits were used and as the purpose of this test was only to determine the feasibility of proceeding further, a series of rapid tests was made with most gratifying and encouraging results. This preliminary experiment proved:

1. That it is possible to insert a thermocouple directly into the brain, the liver, the muscle, the pleural cavity, for a prolonged

period without any notable effect upon the general condition of the animal.

2. That practically any alteration in the condition of the animal —light and deep anesthesia, struggling, shock-producing manipulations, etc.—is accompanied by a measurable change in the temperature of the brain.

3. That the temperature of the brain decreases progressively under ether anesthesia.

4. That the injection of adrenalin produces a characteristic rise and fall in the temperature of the brain closely related to the clinical phenomena—a finding of extreme significance in view of our later studies.

These curves were not plotted, nor was any attempt made to translate the galvanometer readings into actual temperature variations, but the purpose of this preliminary experiment having been attained, we proceeded to devise the essential apparatus for an extensive investigation. We wish at this point again to express our appreciation to Doctor Hyde and Doctor Forsythe for their interest and active coöperation in securing this first evidence.

Apparatus: The essential apparatus consisted of Leeds and Northrup galvanometers of types R and H with especially constructed copper-constantan thermocouples made of 5 mil wire twisted together and soldered. The recording junction was exposed, the leads being separated from each other and protected by concentric glass tubes, the ends of which were joined by dental cement. The junction was kept as small as possible and the protecting glass tubes were of the smallest possible caliber. These tubes were bent into such shapes as could be most easily and firmly secured in the tissue for which each was designed. This is a vitally important point, as closeness and constancy of contact of the thermo-junction with the tissue under examination is essential to the attainment of dependable records.

The use of any metal in the construction of the thermocouples was avoided, for fear it might conduct the heat away from the area of insertion and lead to local cooling. This is an essential precaution in working with an instrument so sensitive to small temperature changes; moreover, it is very important to remove any material which would produce a lag in the response of the indicating instrument to the local changes of temperature.

The "cold" or constant junction of the thermocouple was immersed in a tube of oil suspended in a constant temperature bath, the temperature of which was maintained at 39° C., thus bringing the whole range of temperature in the tissues studied upon the

scale of the galvanometers. As the extreme range of temperatures involved in living rabbit tissues do not exceed 7° C., it is possible to measure variations by the direct deflections of a galvanometer of suitable sensitivity.

The circuit was of very low resistance with all wire connections soldered and symmetrical, and with all contacts non-frictional and of low resistance. The galvanometers were short-circuited when not in use and were protected from extreme deviations.

Calibrations were made immediately after the measurements to which they applied, as there is always a tendency for the instruments to drift from day to day. The calibrations were made by immersing the active junctions along with a standard thermometer in water in a thermos bottle. To avoid error due to the lag in the response of the large bulk of mercury in the standard mercury thermometer, the readings were always made on a falling temperature, as the decrease was so gradual as to minimize error. With this apparatus, temperature variations could be measured to within 0.01° C.

Technic: As far as possible in each group of experiments rabbits of approximately equal size and age were used. This point was not as essential, however, as in our conductivity studies—as in these experiments each animal acted as its own control.

A small hole through the skull over the cortex at the right of the median ridge was made by an especially constructed trephine, the size of the hole being just large enough to admit the glass tube containing the thermo-junction. This tube was bent at an angle, one arm of which was just long enough to enter the brain to a depth of approximately one-third to one-half a centimeter, the other lying along the top of the head. Absorbent cotton was placed over this to eliminate the chance of chilling, the whole being firmly secured in place by strips of adhesive. By this means the thermo-junction was held securely in place even when the animal moved violently.

It was more difficult to secure an immovable junction in the liver, but in most instances this was accomplished by inserting one arm of a right-angled tube through a small opening just below the ribs, and securing it by metal clips through the muscle, with adhesive strips over the skin. By bending the tubes at a right or slightly acute angle, and the use of clips and abundant adhesive, constant contact could usually be secured in any tissue, and by the free use of cotton, complete protection from external chilling was assured.

In the early experiments only one galvanometer was used. As

this precluded the possibility of simultaneous readings of the variations in temperature in different organs, another galvanometer was installed. Thus, two observers could make synchronous readings at 15-second intervals or less.

Seventy-seven rabbits were used in these preliminary studies, consistent records being secured in sixty-three. Any experiment was discarded if at the termination of the experiment any fault in contact was found, the insertion of the thermo-junction being examined at the conclusion of every experiment. As noted above, calibration at the conclusion of each group of experiments and repeated testing of the constant temperature checked the findings throughout.

In these preliminary studies, the effects of various agents and procedures has been observed, the temperature variations in the brain being measured in every instance, in the liver in most of the animals, and in the muscle and thyroid each in two instances.

In the first experiments, as noted above, the galvanometer readings were recorded at 30-second intervals, readings being made alternately when more than one thermocouple was employed. Later by the use of two galvanometers and two observers simultaneous readings were made at 15-second intervals.

Fifteen-second intervals, however, are not sufficiently short to assure the recording of every variation in the temperature of the brain. Frequently a rapid deviation of the galvanometer was observed between the recorded readings, but to assure the greatest possible accuracy by the undivided attention of the observers to the 15-second readings, they were told to allow no other observation to interfere with the correct recording of these—an important injunction in experiments which in many instances were 1½ to 2 hours or more in length, requiring the accurate reading and recording of 300 and more galvanometer readings by each observer. It early became apparent that a method of continuous record is required to register all the temperature changes in the infinitely sensitive brain, for the slightest stimulation of the animal under observation—by the sound of a closing door, a motion of the hand before the eyes, a light touch, etc.—produced a measurable, if but slight and brief, alteration in the brain temperature. In many instances an abrupt rise was observed immediately prior to a struggle which was marked by a sharp fall. This was observed so often that when in a quiet animal the temperature of the brain rose abruptly, a struggle was expected.

The variation in the temperature of the brain which preceded and accompanied a struggle occurred in such rapid succession that

it was impossible in every instance to synchronize the event and the galvanometer reading with certainty. The apparent variations in the nature of the response to certain stimuli are undoubtedly due to this difficulty which can only be obviated by continuous records.

In many cases various forms of stimulation were applied to the same animal. In the following presentations, therefore, instead of following the usual method of presentation of protocols, the findings will be summarized according to the various forms of stimulation employed.

Especial appreciation is due to Donald D. Forward for his efficient coöperation in many details of this research and to George Harris Crile for his patient and accurate readings of the galvanometer.

SUMMARY

1. By the use of especially constructed thermocouples it is possible to measure temperature variations in living tissues to within 0.01° C.

2. By the described apparatus and technic the progress of functional changes in the brain and other tissues in stimulation and exhaustion from various causes has been observed, and the findings correlated with the histologic changes and the alterations in electric conductivity established by previous researches.

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THERMO-ELECTRIC STUDIES OF TEMPERATURE VARIATIONS IN ANIMAL TISSUES

II. Effects of Anesthesia; Electrical Stimulation; Abdominal Trauma; Exposure of Viscera; Excision of Organs; Acid; Alkali; Strychnin; Diphtheria Toxin

By George W. Crile and Amy F. Rowland

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Under the methods described in the preceding section of this report, animals were subjected to stimulation and exhaustion from various agents and the temperature variations produced by each were observed and recorded.

1. *Inhalation anesthesia.* Inhalation anesthesia—ether or nitrous oxid—produced a continuously progressive decrease in the temperature of the brain and the liver, this decrease being much

greater in the case of ether. In the course of prolonged ether anesthesia the temperature of the brain and of the liver may decrease from 1½ to 2° or the decrease may amount even to 4°; while under even prolonged nitrous oxid oxygen anesthesia, the decrease in temperature, though progressive, is so slight as to be practically negligible. The initial stage (stage of excitement) both of ether and nitrous oxid anesthesia is marked by a slight increase in the temperature of the brain. This initial increase in temperature corresponds to the hyperchromatic stage described in our histologic studies of the brain cells and to the increased electric conductivity of the brain which we found was present in the first stage of both ether and nitrous oxid anesthesia.

2. *Electrical stimulation.* In this group of experiments the current from a single dry cell attached to an induction coil was used, the coil being so adjusted as to produce a sharp tingling of the tongue with the terminals about 0.5 cm. apart. The terminal wires were applied directly to the sciatic nerve, the sciatic nerves on both sides being exposed. On each side stimulation was applied first to the unblocked nerve which was then novocainized and the current again applied. The animals were under ether anesthesia throughout.

Stimulation of the unblocked nerve produced a change in the temperature of both the brain and the liver *in opposite directions.* In certain cases the first stimulation produced an increase in the temperature of the brain and a decrease in the temperature of the liver; while the like stimulation of the opposite nerve produced a decrease in the temperature of the brain and an increase in the temperature of the liver, these opposite effects being especially marked when the first response had been particularly severe. After complete blocking of the nerve there was but slight or no response to stimulation of the sciatic nerve.

3. *Abdominal trauma, exposure of viscera, etc.* Every injury of the abdominal wall or shock-producing manipulation of the peritoneum or intestine was registered by an alteration in the temperature of the brain. These variations were especially manifested during the manipulations essential to excision of the adrenals or to ligation of the liver.

Exposure of the viscera produced a precipitate decrease in the temperature of the brain. The like fall in the temperature in the liver which in part may be attributed to the direct exposure, may in part be due to other causes.

Hot water in stomach: The introduction of hot water into the stomach through a stomach tube increased the temperature of the

brain and the liver, *the increase in the temperature of the brain occurring first.*

In some instances, the temperature of the liver did not begin to increase until a minute or more after the beginning of the increase in the brain was noted.

4. *Excision of organs. Hepatectomy* was followed by a continually progressive fall in the temperature of the brain which was unchecked by any therapeutic measure. The rapidity of the decrease, however, varied according to the condition of the animal and the amount of trauma produced by ligation of the liver.

Adrenalectomy produced a rapid decrease in the temperature of the brain, although the short duration of life in two of the three animals in which adrenalectomy was done makes it impossible to determine to what degree this decrease was due to the trauma of the operation.

5. *Acid.* In one experiment the intravenous injection of hydrochloric acid (1 cc. of 10 per cent solution) was immediately followed by an abrupt rise in the temperature of the brain amounting to 0.7° C. with an equally abrupt fall to 0.56° C. below the point at which the acid was injected; from this point there was a rapid and precipitous decline until death which occurred 5 minutes after the injection. The liver showed no response to the acid injection and at the time of death the temperature of the liver was but 0.46° C. below the point at which the acid was injected, while the total decline in the temperature of the brain amounted to 1.63° C.

6. *Alkali.* In one experiment 8 cc. of a saturated solution of sodium bicarbonate were injected intravenously. During the injection, which lasted 4 minutes, the temperature of the brain rose 0.5° C. There followed a fall to a point 0.5° below the point at which the injection was started, this period lasting for 8 minutes. During the following 10 minutes there was a further gradual decrease of 0.33°. Ether was then given, the abdomen opened, viscera exposed and extreme shock-producing manipulations were made. Although the fall in brain temperature was accelerated thereby the picture does not correspond to that produced by like exposure and trauma in other experiments. The animal lived for 15 minutes after the abdomen was closed, and was finally sacrificed when the temperature of the brain had reached the low point of 34° C. As after the injection of hydrochloric acid, the *liver* showed no response to the injection of sodium bicarbonate, its temperature declining but slowly until the viscera were exposed.

7. *Strychnin.* The effects of strychnin injection upon the temperature of the brain varied in relation to the clinical effects. In

an animal in which typical convulsions occurred there were correspondingly great variations in the brain temperature; while in another in which the muscular contractions were less marked the variations in the temperature of the brain were correspondingly less than in the former instance. In no instance was the temperature of the liver affected by the injection of strychnin.

In two animals under nitrous oxid anesthesia the injection of strychnin produced but a slight variation in the brain temperature, although in one of these there were strong convulsions.

8. *Diphtheria toxin.* The temperature of the brain and liver was watched continuously for hours after the injection of diphtheria toxin. No significant change in the liver was noted but there were variations in the temperature of the brain. In one instance, on the day after the injection of the toxin, the animal was placed under ether anesthesia when the brain showed a precipitate decline in temperature, death occurring 21 minutes after the anesthesia was started. The rectal temperature when the toxin was injected was 38.5° C. At 8:00 o'clock on the following morning it was 41.1°, and 2¾ hours later it had fallen to 40.8°. Eight minutes before death it was 38.8°.

SUMMARY

1. The progress of exhaustion from any cause—continuous ether anesthesia, adrenalectomy, physical trauma—is marked by a progressive decrease in the temperature of the brain and the liver, the rapidity of which bears a direct relation to the rate at which the degree of exhaustion advances.

2. The stage of excitement of ether and of nitrous oxid anesthesia is marked by an increase in the temperature of the brain.

3. After hepatectomy the temperature of the brain declines progressively until death, the resultant curve corresponding closely to that produced by continuous ether anesthesia.

4. Muscular activity, either voluntary or produced by direct electric stimulation of a nerve, is accompanied by rapid alterations in the temperature of the brain and the liver corresponding to the phases of the muscular activity—these alterations, however, being in opposite directions.

5. No alteration in the temperature of the liver appears to be produced by the injection of strychnin, of an acid or of an alkali, although marked and characteristic changes, corresponding in each case to the clinical phenomena, are produced by each in the temperature of the brain.

6. Exposure of the viscera and abdominal trauma alike produce a rapid fall in the temperature of the brain and the liver, the change in the latter being in part but not entirely accounted for by the direct chilling of the liver substance.

7. The restorative effect of the introduction of hot water into the stomach is marked by an immediate elevation of the temperature of the brain which measurably precedes—in some instances by a minute or more—the resultant elevation in the temperature of the liver.

8. The lowered resistance to inhalation anesthesia produced by an acute infection is illustrated by the rapid decline in the temperature of the brain of an animal subjected to ether anesthesia 24 hours after an intravenous injection of diphtheria toxin.

THERMO-ELECTRIC STUDIES OF TEMPERATURE VARIATIONS IN ANIMAL TISSUES

III. Adrenalin

By George W. Crile and Amy F. Rowland

From the *American Journal of Physiology*, Vol. 62, No. 2, October, 1922

In section II of this presentation, we have reported a series of studies of the effects of various agents upon the temperature of the brain and the liver as indicated by measurements by means of especially devised thermocouples.

Early in the progress of these studies it became evident that the response of the brain to the injection of adrenalin was so uniformly manifested in normal animals by typical temperature changes that we adopted the temperature response of the brain to adrenalin as a kind of unit of comparison in a series of experiments, the findings in which appear to be so significant that we make them the subject of a separate report.

Four-tenths of a cubic centimeter per kgm. of 1:1000 Parke, Davis & Co.'s adrenalin was the dose employed throughout these experiments after a series of tests had shown that this dosage gave the most uniform response in normal rabbits.

Normal response of the brain to adrenalin. In normal rabbits the intravenous injection of adrenalin was followed by a rise in

the temperature of the brain which in most instances amounted to between 0.3 and 0.5° C., although in some instances an even greater rise occurred. The rise started immediately after the injection, the highest point being reached in from 6 to 10 minutes, with an approximately equally protracted return to the temperature level preceding the injection.

Response of the brain to adrenalin in anesthetized animals. In rabbits under ether anesthesia the temperature of the brain rose abruptly upon the injection of adrenalin, and the rise was usually greater than in normal animals. Under *nitrous oxid anesthesia,* on the other hand, there was slight or no response to the injection of adrenalin or the response was atypical. In one experiment the injection of adrenalin in an animal anesthetized with urethane caused an abrupt rise in the temperature of the brain followed by a delayed decline.

Response of the brain to adrenalin in iodized animals. The injection of adrenalin in animals which had been iodized by the intraperitoneal injection of iodoform produced an abrupt increase in the temperature of the brain which was greater than that observed in any other condition—in one instance amounting to 1.72° C. within 4 minutes with an equally abrupt fall.

Response of other organs than the brain to the injection of adrenalin. The *liver* is apparently irresponsive to the injection of adrenalin as far as is indicated by temperature variations.

The *thyroid gland,* on the other hand, showed a response to adrenalin in temperature variations which in some cases approximately paralleled the temperature changes in the brain.

The temperature of *voluntary muscle* apparently is not changed by adrenalin injection.

The effect of hepatectomy upon the response of the brain to adrenalin. Repeated observations appeared to demonstrate that after hepatectomy the power of the brain to respond to adrenalin is diminished or lost.

By accident, however, it was found that if even a very small portion of the liver remained patent to the circulation, the brain would register its usual response to adrenalin by the typical increase in temperature. In this experiment, it appeared at first that the premise we had thought established by preceding hepatectomies was disproved, until autopsy revealed that a small lobe of the liver had not been included in the ligation. Subsequent experiments have verified this finding.

A single experiment was performed to see whether or not lack of response of the brain of a hepatectomized animal was due to

lack of glucose. In this experiment, at least, no effect upon the response to adrenalin was produced by the intravenous injection of a solution of glucose in a hepatectomized animal.

The effect of thyroidectomy upon the response of the brain to adrenalin. Forty-eight hours after the removal of both thyroids the injection of adrenalin was followed by a delayed and slight rise in the temperature of the brain.

SUMMARY

1. The temperature of the *brain* and of the *thyroid* was increased by adrenalin.
2. The temperature of the *liver* and of *voluntary muscle* was not affected by the injection of adrenalin.
3. In the *absence of the liver* the injection of adrenalin produced a diminished or no change in the temperature of the brain.
4. In the *absence of the thyroid* the reaction of the brain to adrenalin was diminished.
5. In *iodized* animals the reaction of the brain to adrenalin appeared more promptly and was greater than in normal animals.
6. In animals under *ether* anesthesia the reaction of the brain to adrenalin was greater than in normal animals.
7. In animals under *nitrous oxid* anesthesia the reaction of the brain to adrenalin was delayed and diminished.

GENERAL CONCLUSIONS

1. The variations in the temperature of animal tissues which accompany variations in function can be measured in the living animal by thermo-electric methods. In these studies the variations in temperature were measured to within 0.01° C.
2. Variations in temperature not only provide a further criterion whereby to identify the organs and tissues which are concerned in the production of vital phenomena, but also suggest the interrelation of the functions of these organs and tissues.
3. The variations in the temperature of the brain under various conditions parallel variations in the histologic picture and in the electric conductivity of the brain under the same conditions.
4. Of particular significance are the findings, (a) that in voluntary muscular activity and as a result of the direct electric stimulation of a nerve the temperature of the brain and of the liver varies in opposite directions; (b) that upon the introduction of hot water

into the stomach the reaction of the brain in increased temperature precedes that of the liver; (c) that the temperature of the liver is but little altered or is unchanged by the injection of adrenalin; of strychnin; of an acid; of an alkali.

5. The findings in these studies support the conclusions (a) that the brain is the tissue upon which depend the reactions of the organism to stimulation; (b) that the thyroid and the adrenals play essential parts in the production and maintenance of these reactions; (c) that in the performance of its function the brain is indissolubly linked with the liver.

6. The lack of response of the brain to adrenalin in the absence of the liver together with the opposite reactions of the brain and the liver may form vital links in the chain of evidence whereby we may determine the function of each in the electro-chemical operation of the animal mechanism.

APPLICATION OF BIOPHYSICAL RESEARCH TO MEDICAL PROBLEMS

By G. W. Crile, M.D., and Hugo Fricke, Ph.D.

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The research, part of which is reported in this paper, is a further extension of previous studies undertaken for the purpose of ascertaining to what extent biophysical methods can be used in the investigation and interpretation of medical problems. Our observations of the effect of certain agencies such as adrenalin, anesthetics, stimulants, electrolytes, etc., on the temperature of various organs and tissues of the body have been made with the thought that if the effect of these influences should prove to be uniform and consistent with biological facts, these studies would lead to a wider use of biophysical methods. There are many other studies which will be reported in a later paper in which we expect to set forth an interpretation of our findings. At the present time we wish only to make known the facts which have appeared in these investigations.

Several similar attempts to study temperature changes in the tissues of animals under different conditions have been carried out in the past. In addition to the literature reported in a previous pub-

lication, we may especially mention the work of Mosso,[1] who measured the temperature changes by means of a very sensitive mercury thermometer. He believed that he had found that a very great change in the metabolism of the brain followed the injections of certain drugs, among them being absinthe and strychnin. Hill and Nabarro,[2] however, criticized Mosso's work and made evident that his results were due mainly to the action of the drugs upon the blood circulation.

The amount of oxygen used in the metabolic processes in a state of rest and of excitation is known for many of the body organs in which excitation usually causes a several-fold increased consumption. How the energy corresponding to this oxygen consumption is used, how much is transformed into heat, and how much is used by the organ in the performance of its functions, are questions whose answers have not been directly determined for most organs. In the case of a muscle at work, A. V. Hill[3] has found that there is a maximum efficiency of fifty per cent. From an estimation of the work done by the organs it is safe to assume that for most organs the major portion of the chemical energy obtained through the oxygen consumption is directly transformed into heat. The chemical energy of the oxygen consumed by an organ under excitation corresponds to a temperature increase of a few tenths of a degree Centigrade per minute. The magnitude of this change indicates the feasibility of employing thermocouples for the temperature measurements in the study of metabolic processes.

In the studies reported here our attention has been directed especially to the measurement of the temperature changes which occur in the brain. As compared with most other organs, the oxygen consumption of the brain is large. It seems probable that the energy corresponding to this consumption is not directly converted into heat for the sole purpose of maintaining the brain temperature, but that it is primarily used by the brain in its special activities, finally appearing as heat in the brain or in other parts of the body. If this is so we would expect that activation of the brain would be accompanied by temperature changes large enough to be recorded.

It is evident, however, that changes in the circulation of the blood, due to vaso-constriction and vaso-dilation in the different parts of the body, must be an important factor in the production

[1] Mosso, *Proc. Roy. Soc.*, London, 1892.
[2] Hill, L., and Nabarro, D. N., *Jour. Physiol.*, 1895, xviii, 218.
[3] Hill, A. V., *Jour. Physiol.*, 1913, xlvi, 435.

of the temperature changes in an organ. This fact makes the interpretation of the records of temperature change quite complicated.

Experimental Technic.—The temperature changes in the organs studied were measured by means of copper-constantan thermocouples combined with mirror galvanometers. The time of vibration of the galvanometers was about seven seconds. The galvanometer deflections were reflected on a common scale, the resistances in each circuit being so adjusted that a deflection of one division on the scale (equal to two millimeters) corresponded to a temperature change of one one-hundredth of a degree Centigrade. The scale covered a temperature range of 6° C. A specially designed potentiometer made possible the immediate introduction into each thermocouple circuit of an electromotive force corresponding to a temperature difference of 4° C., so that continuous temperature readings could be made over a range of 14° C.

One junction of each thermocouple was inserted in a constant temperature bath, constant to within one one-hundredth of a degree Centigrade, the other junction being inserted in the organ under investigation. In most measurements one thermocouple was inserted in the brain and one in some other organ or tissue. In some cases, however, three thermocouples were employed.

In order to avoid the influence of bioelectric, or galvanic forces, it is necessary to insulate thoroughly the wires that are inserted in an organ. This was done by enameling the wires and coating them with de Khotinsky cement.

A special metal holder was constructed for the thermocouple that was inserted in the brain. The wires, constantan No. 35 and copper, No. 40, were passed through a hard rubber cylinder, the thermojunction extending about one centimeter beyond the end of the rubber, the exposed portion being covered with de Khotinsky cement which served also to cement the thermojunction in place.

The skull of the rabbit was trephined to make an opening 6 mm. in diameter and the holder clamped in place, the hard rubber rod with the thermocouple junction being then inserted. The depth of penetration of the brain varied in different experiments from 2 mm. to about 8 mm. The trephined opening was made to the right of the mid-line on a level with the posterior superciliary ridge.

The thermocouples inserted in other organs also were constructed of No. 35 constantan and No. 40 copper wire. The wires were soldered together, the constantan wire extending about three inches beyond the junction. By passing this free end through a

needle the junction could be readily drawn into the desired position within the tissue.

We wish to express our appreciation of the coöperation of Mr. Seitz of the Electromechanical Engineering Department of the Cleveland Clinic in the construction of the apparatus described above.

In a later paper we propose to discuss the relative rôles played in these temperature changes by alterations in the blood circulation, in the blood temperature, and in the metabolism of the organ.

Inhalation anesthesia.—Ether in its first stages frequently produced an increase in the temperature of the brain. As the depth of the anesthesia was increased the temperature fell.

Nitrous oxid as compared with ether showed a less marked change in the temperature and fewer flunctuations, thus giving a more stabilized curve.

Chloroform showed an initial rise in temperature corresponding to that produced by ether. When full anesthesia was established the temperature fell.

Adrenalin: A number of observations have been made of the effect of the intravenous injection of adrenalin upon the temperature of the brain, the liver, the thyroid gland, the adrenal glands, the spleen, the intestines, the kidneys, and the muscles. The uniform dosage employed throughout was the same as that used in previous researches, viz., 0.4 cc. per kg. of 1:1000 adrenalin chlorid (P. D. & Co.).

In every case, the brain showed a very characteristic rise in temperature, the temperature increase continuing for from ten to fifteen minutes and amounting, on an average, to about 0.7° C. The other organs usually showed an effect just opposite to that in the brain, the minimum temperature, however, usually occurring a few minutes later than the corresponding maximum for the brain.

In several cases the temperature of the spleen and of the intestine fell markedly, in some cases as much as two degrees or more.

In all the above experiments the thermocouple was inserted in the gray matter of the brain and in every case a rise in temperature was noted. It was found, however, that when the thermocouple was placed in the white matter, no change in temperature occurred after the injection of adrenalin.

Amyl Nitrite: The inhalation of amyl nitrite produced a marked rise of 1.1° C. in the brain temperature, the liver showing

no decided effect, excepting a slight, continuous decrease in temperature.

Electrolytes: The action of sodium and calcium chlorid has an important theoretical interest. The well-known antagonistic relation existing between sodium chlorid and calcium chlorid was strikingly illustrated. The doses given were 2 cc. of a saturated solution—36 per cent—of sodium chlorid and 1 cc. of a 10 per cent solution of calcium chlorid.

Sodium Cyanid. The action of a strong poison was shown by various injections of sodium cyanid. The injection of 0.001 *N* solution caused a slight rise of temperature, corresponding to the stage of excitement. The injection of 0.01 *N* solution produced a state of depression, while an injection of 0.1 *N* solution caused an immediate drop in temperature followed by a marked rise during a period in which violent tremors and convulsions were occurring. During these convulsions the temperature fluctuated over a range of 0.1° C. The result of the injection of still stronger doses was an immediate, rapid decrease in the temperature of the brain followed in a few minutes by death.

SUMMARY

1. By means of direct measurements of the variations in the temperature of animal tissues, new light may be thrown upon the action of any agent upon the organism.

2. The observations thus far made are consistent with the clinical observations, and with the findings in other forms of physiological research.

3. The opposite effects of the injection of adrenalin upon the brain and upon other organs and tissues demand especial consideration.

4. The use of the biophysical method of measuring variations in function opens the way to further applications of biophysical methods in the study of physiological problems.

BIOPHYSICAL STUDIES OF THE EFFECTS OF VARIOUS DRUGS UPON THE TEMPERATURE OF THE BRAIN AND THE LIVER[1]

I—STRYCHNIN, II—MORPHIN, III—BROMIDS, IV—CURARE, V—ATROPIN. VI—CAFFEIN, VII—ALCOHOL

By George W. Crile, Amy F. Rowland and S. W. Wallace

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In previous reports of our thermo-electric studies of temperature variations in animal tissue we have noted that the injection of adrenalin in normal animals was uniformly followed by a rise in temperature of about 0.5° C., the periods of rise and fall being practically uniform, and the curve being completed in approximately ten minutes.[2] If further studies should prove that we are correct in our assumption that variations in the temperature of the brain indicate alterations in its oxidative power, then this response to adrenalin would be an indication of the oxidative power of the brain and it should be possible to compare the effects of various agents upon the oxidative power of the brain by measuring the response of the brain to the injection of adrenalin after the injection or application of those agents. In the following studies therefore the effects of various drugs upon the temperature of the brain and also of the liver have been observed, the variations in temperature being measured by means of specially constructed thermocouples.

STRYCHNIN

In a previous report [3] we have stated that the effects of strychnin upon the temperature of the brain vary in relation to the clinical

[1] Read before the Pharmacological Society of the Federation of American Societies for Experimental Biology, Toronto, Ont., December 27-29, 1922.

[2] *Amer. Jour. Physiol.*, 1922, lxii, 370-382; *Proc. Amer. Phil. Soc.*, 1922, lxi, 237-245.

[3] *Amer. Jour. Physiol.*, 1922, lxii, 349-369.

effects. That is, in an animal in which typical convulsions occurred there were correspondingly great variations in the brain temperature while in another in which the muscular contractions were less marked the variations in the temperature of the brain were correspondingly less than in the former instance. In no instance was the temperature of the liver notably affected.

For the further interpretation of these findings, in view of the conclusions summarized above, 6 animals were given a standard dose of adrenalin (0.4 cc. of a 0.001 per cent solution—P. D. & Co.—per kilogram) after the injection of varying doses of strychnin. The resultant effects upon the temperature of the brain and the liver are shown in Table 1. The interesting feature of these observations is the opposite effect of the injection of adrenalin in the presence of strychnin upon the temperature of the brain and of the liver. The rise in the temperature of the brain after the first dose of adrenalin varied from 0.25 to 1.2°C; the fall in the temperature of the liver varied from 0.4 to 1.8°C. The marked fall in the temperature of the liver is noteworthy in contradistinction to the lack of effect of strychnin alone upon the temperature of the liver which has been noted above.

MORPHIN

In view of the diversity of opinion regarding the influence of morphin on the consumption of oxygen and of the known fact that morphin acts primarily upon the higher centers in the cortical portion of the brain, it seemed of especial importance to study the effect upon the temperature of the brain of the injection of adrenalin in the presence of narcotization by morphin. Five experiments were performed, the results of which are given in Table 2. A study of this table shows that the amount of increase in the temperature of the brain after the injection of adrenalin was in direct relation to the depth of narcosis of the rabbit, varying from 0 and 0.05 to 0.2°C. in deeply narcotized rabbits, and from 0.25°C. in a slightly narcotized rabbit to 0.5°C. in a rabbit in which the morphin produced scarcely any clinical effects. The effect of adrenalin upon the temperature of the liver was in the opposite direction to that upon the temperature of the brain and in general this effect also was in direct relation to the depth of the narcosis. In 4 cases no response was noted in the liver temperature; but in one very strongly narcotized rabbit a very marked fall in temperature was noted after each of 2 injections of adrenalin—of 0.8 and 0.65°C., respectively.

BROMIDS

In 6 experiments 15 cc. of a 20 per cent solution of sodium bromid was injected intravenously on each of three consecutive days. At varying periods after the injection on the third day a standard dose of adrenalin was injected. No variation from the normal response to adrenalin was observed. There was no notable effect upon the temperature of the liver.

CURARE

It appeared that it might be of interest to establish the temperature variation in the brain in the absence of any metabolic activity in the voluntary muscular system. Since curare acts specifically on the neuro-muscular plates its injection would cut down the metabolism of the muscular system as a whole. In 2 animals therefore 10 mgm. of a 0.5 per cent solution of curare was injected intramuscularly. Artificial respiration was established and the usual injection of adrenalin was given. The only alteration in the response of the brain was that the temperature rise was somewhat delayed and was less than the normal *average* response but not less than the response observed in some normal animals. There was no effect upon the temperature of the liver.

ATROPIN

Since atropin produces an increased blood pressure as the result of the contraction of the arteries of the splanchnic area and to some extent produces peripheral vasodilation, it would appear that in all probability the blood supply to the brain would be increased by the injection of atropin. If the increased temperature of the brain which follows the injection of adrenalin in normal animals is due to an increased blood supply to the brain then it would follow that the injection of adrenalin after the injection of atropin would produce a greater rise in the temperature of the brain than that observed in normal animals. Three experiments were performed in which no variation from the normal response was noted, the rise in temperature in the 3 rabbits utilized being respectively 0.6, 0.45 and 0.4°C. In contradistinction to other experiments, however, a gradual rise in the temperature of the liver of between 0.3 and 0.4°C. was noted.

The effect of strychnin upon the oxidative power of the brain and the liver as indicated by temperature changes after the injection of adrenalin

EXPERIMENT NUMBER	STRYCHNIN DOSAGE		TIME AFTER STRYCHNIN ADRENALIN WAS GIVEN		MAXIMUM RISE OF BRAIN TEMPERATURE	DURATION OF RISE IN BRAIN TEMPERATURE	MAXIMUM FALL OF LIVER TEMPERATURE	DURATION OF FALL OF LIVER TEMPERATURE	
					°C.	minutes	°C.	minutes	
I	Dose I	1/60 grain—3 doses (intramuscular) at 10 minute intervals	Dose I	8 minutes after last dose of strychnin	+ 0.25	6	— 0.40	9	Convulsions
			Dose II	21 minutes after last dose of strychnin	+ 0.10	2	— 0.30	5	
II	Dose I	1/20 grain (intramuscular)	Dose I	5 minutes after last dose of strychnin	+ 0.6	7	— 0.40	13	
			Dose II	44 minutes after last dose of strychnin	+ 1.0*	14	— 0.17	8	
III	Dose I	1/100 grain (intravenous)	Dose I	5 minutes after dose I of strychnin	+ 0.5	6	— 1.15	5	
	Dose II	1/100 grain (intravenous)	Dose II	5 minutes after dose II of strychnin	+ 0.6	9	— 0.8	7	
IV	Dose I	1/20 grain (intramuscular)	Dose I	5 minutes	+ 0.42	10	— 0.5	10	Convulsions
V	Dose I	1/15 grain (intramuscular)	Dose I	6 minutes	+ 0.45	9	— 1.8	10	Convulsions
VI	Dose I	1/15 grain (intramuscular)	Dose I	13 minutes	+ 1.2	14	— 0.7	16	Died in convulsions

The dose of adrenalin in each experiment was 0.4 cc. of 1:1000 (P. D. & Co.) per kilogram.
* This followed marked fall in brain temperature after first dose of adrenalin.

TABLE 2

The effect of morphin upon the oxidative power of the brain and the liver as indicated by temperature changes after the injection of adrenalin

EXPERIMENT	WEIGHT OF RABBIT	DOSE OF MORPHIN SUBCUTANEOUSLY	DOSE OF ADRENALIN INTRAVENOUSLY		PERIOD BETWEEN MORPHIN INJECTION AND INJECTION OF ADRENALIN	BRAIN		LIVER		STATE OF NARCOSIS
						Total rise after adrenalin	Duration of rise after adrenalin	Total fall after adrenalin	Duration of fall after adrenalin	
	pounds	*grains*		*cc.*		° *C.*	*minutes*	° *C.*	*minutes*	
I	5½	2	Dose I	1.0	38 min.	+ 0.2	5	0	0	Deep
			Dose II	1.0	1 hr. 15 min.	+ 0.2	6	— 0.1	6	Deep
			Dose III	1.0	3 hrs. 50 min.	+ 0.17	6	— 0.05	4	Deep
II	5½	2	Dose I	1.0	1 hr. 5 min.	+ 0.15	5	— 0.05	4	Deep
			Dose II	1.0	3 hrs. 22 min.	+ 0.4	8	— 0.22	11	Slight (rabbit nearly recovered)
III	7	2	Dose I	1.25	1 hr. 8 min.	+ 0.5	10	— 0.8	9	Very slight
			Dose II	1.25	3 hrs. 22 min.	+ 0.4	11	— 0.65	9½	Practically none
IV	5½	2	Dose I	1.0	1 hr. 5 min.	+ 0.05	5	0	0	Deep
			Dose II	1.0	1 hr. 38 min.	+ 0.2	5	0	0	Fairly deep
			Dose III	1.0	2 hrs. 44 min.	+ 0.25	4	0	0	Partial (rabbit struggled frequently)
V	5	2	Dose I	1.0	42 min.	+ 0.3	6	Liver readings not made		Dose I: partial (rabbit had not fully gotten effect of morphin).
			Dose II	1.0	1 hr. 20 min.	0	0			Dose II: very deep (pinching of femoral nerve gave practically no response)

CAFFEIN

Since caffein stimulates especially the cortical centers of the brain, it was suggested that it might be of value to note its effect upon the temperature of the brain. Two experiments were performed in which each rabbit was given 2 subcutaneous doses of caffein, of 0.5 grain each ten minutes apart. The subsequent injection of adrenalin was followed by a rise in temperature which did not vary in amount from that observed in normal animals but did vary from the normal response in its abruptness. That is, the rise began while the injection of adrenalin was being given and the temperature rose to the maximum point with extreme rapidity. No notable change in the temperature of the liver was observed.

ALCOHOL

Variance of opinion as to the physiologic effect of alcohol suggested the use of this agent in this series of studies. In 1 rabbit 20 cc. of a 50 per cent solution of alcohol was introduced into the stomach and in 2, 8 cc. of a 25 per cent solution was given intravenously. In each instance the temperature of the brain fell with a rapidity corresponding to the fall in an animal in a moderate degree of shock. Periods of muscular activity occurred at almost equal intervals, each causing a momentary rise in the temperature of the brain and the liver amounting to about 0.07°C. The injection of adrenalin in these animals caused a rise in the temperature of the brain corresponding to that in normal animals with an abrupt fall after the maximum point had been reached to a point which in one instance was 1.7 degrees below the temperature when the adrenalin was given. In another case the animal died suddenly when the temperature of the brain had fallen to a point 0.35 degrees below that at which the adrenalin was given.

SUMMARY

1. It is assumed that the effect of the injection of adrenalin upon the temperature of the brain in normal animals can be used as a unit of measurement whereby to estimate the effect of an agent upon the oxidative power of the brain.

2. From these experiments it would appear that the alteration in the temperature of the brain following the injection of

adrenalin is not notably affected by the effect of the agent upon the blood supply of the brain.

3. The following observations are of especial significance:

a. When adrenalin is injected in the presence of morphin, the temperature response of the brain is diminished in direct relation to the depth of narcosis.

b. The injection of adrenalin in the presence of strychnin produces not only a characteristic rise in the temperature of the brain but also a marked decrease in the temperature of the liver.

c. Alcohol of itself alone produces a fall in temperature corresponding to that observed in rabbits in shock, while the injection of adrenalin in these animals produces a characteristic rise in temperature; this rise is followed by a fall which exceeds that observed in normal rabbits.

Note: Since the presentation of this paper a further series of experiments has been initiated, in which thermocouples are placed within the jugular vein and the carotid artery. The first experiment is cited here only as a preliminary report of an investigation which may aid in the interpretation of the studies summarized above. In this experiment, *after each injection of adrenalin the temperature of the blood within the vein rose above that of the blood within the artery.*

THE EFFECT OF ASPHYXIA UPON THE ADRENAL OUTPUT AS DEMONSTRATED BY VARIATIONS IN THE TEMPERATURE OF THE BRAIN

By George W. Crile, Amy F. Rowland and S. W. Wallace

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In view of the findings by Cannon[1, 2] and by other investigators that the secretion of epinephrin is increased by asphyxia, an observation which had also been made by one of us in a previous research; and since it had been demonstrated in the biophysical laboratories of the Cleveland Clinic that the injection of adrenalin in normal animals produces a typical increase in the temperature of the brain, it seemed that it would be of interest to measure the temperature of the brain during asphyxia, both in animals with intact adrenals and in animals from which the adrenals had been removed. A series of eleven experiments was performed (Table 1).

TABLE 1

The effect of asphyxia upon the output of epinephrin as indicated by variations in the temperature of the brain

EXPERIMENT	WEIGHT OF RABBIT	PRELIMINARY PROCEDURE	PERIOD OF ASPHYXIA I	RISE IN TEMPERATURE OF BRAIN	PERIOD OF ASPHYXIA II	RISE IN TEMPERATURE OF BRAIN	PERIOD OF ASPHYXIA III	RISE IN TEMPERATURE OF BRAIN	RISE OF BRAIN TEMPERATURE AFTER INJECTION OF ADRENALIN
	lbs.		*min.*	*°C*		*°C.*		*°C*	
1. Normal			5	+0.51	4½ min.	+0.19	3½ min.	+0.13	+0.67°C.
2. Normal	4½		7¾	+0.98	7½ min.	+0.84			
3. Morphin	6	Morph. sulph. gr. 2½ in 2 doses—Gr. 2, 1 hr. and Gr. ½, —½ hr. before first asphyxia	5¾	+0.04	(3 hrs. 39 min. after morphin dose 2) 4½ min.	+0.26	(3 hrs. 53 min. after morphin dose 2) 4 min.	+0.21	Dose 1 5 min. after asphyxia I +0.29°C. dose 2 immediately after asphyxia III +0.25°C
4. Strychnin	6	Strych. sulph. gr. $\frac{1}{15}$ 5½ min. before asphyxia	5	+0.42					
5. Strychnin	5	Strych. sulph. gr. $\frac{1}{15}$, 4 min. before asphyxia	3½	+0.4					
6. Adrenalectomy	5½	Double adrenalectomy under ether anesthesia 9 min. before asphyxia	3¾	*Fall* −0.28					+2.09°C.
7. Adrenalectomy	5½	Double adrenalectomy under ether anesthesia 11 min. before asphyxia	4	*Fall* −0.18					+1.52°C
8. Adrenalectomy	6¼	Double adrenalectomy under ether anesthesia 10 min. before asphyxia	2¼	*Fall* −0.12	1 min.	*Fall* −0.09			+1.0°C.
9. Abdominal shock	5¾	Abd. manip. and exposure approximately equiv. to that of removing adrenals 13 min. before asphyxia	11	+0.64	7 min.	+0.44			

TABLE 1—*Concluded*

EXPERIMENT	WEIGHT OF RABBIT	PRELIMINARY PROCEDURE	PERIOD OF ASPHYXIA I	RISE IN TEMPERATURE OF BRAIN	PERIOD OF ASPHYXIA II	RISE IN TEMPERATURE OF BRAIN	PERIOD OF ASPHYXIA III	RISE IN TEMPERATURE OF BRAIN	RISE OF BRAIN TEMPERATURE AFTER INJECTION OF ADRENALIN
	lbs.		*min.*	°*C.*		°*C.*		°*C.*	
10. Abdominal shock	5	Abd. manip. and exposure approximately equiv. to that of removing adrenals 12 min. before asphyxia	4	+0.36	2 min.	+0.27	4 min.	+0.2	
11. Abdominal shock partial adrenalectomy	5½	(See note) Operation completed 11 min. before asphyxia	5	+0.37	7¾ min.	+0.47			

Note. This was supposed to be a complete double adrenalectomy; the rise in temperature accompanying asphyxia led to an autopsy which showed one-third of right adrenal *in situ*.

In two normal animals the temperature of the brain during the period of asphyxia rose 0.51°C., and 0.98°C. respectively. Subsequent periods of asphyxia in these animals were also accompanied by a rise in brain temperature to a lesser degree. One animal was heavily narcotized with morphin. Asphyxia while the animal was deeply narcotized caused an increase in the temperature of the brain of only 0.04°C. Three hours later, however, when the period of narcotization was nearly passed the temperature of the brain during the period of asphyxia rose 0.26°C. In marked contrast to the effect of asphyxia in animals narcotized by morphin was the effect in animals which had received a preliminary dose of strychnin. In each of two animals which had received $\frac{1}{15}$ of a grain of strychnin five minutes before each was subjected to asphyxia, the temperature of the brain rose 0.4° C. In three animals the adrenals were removed, the operation being completed ten minutes before the period of asphyxia. In each of these animals the temperature curve of the brain was unaltered by the asphyxia. The injection of adrenalin in each of these caused an abrupt and large increase in the temperature of the brain of from 1 to 2.09°C. Since in each of these last three animals

the shock of the operation was necessarily great and the temperature of the brain was falling steadily, it was suggested that the lack of response to the asphyxia might be due to the degree of shock in each animal. In two animals, therefore, under ether anesthesia for the same period as that required for adrenalectomy, the abdomen was opened and the intestines were exposed and manipulated. At the conclusion of the manipulation the temperature of the brain of each of these animals was falling at approximately the same rate as in animals in which the adrenals had been removed; but in the two animals subjected to shock alone during asphyxia the temperature of the brain rose 0.64° C. and 0.36° C. respectively. In another animal in which an attempt was made to perform a complete double adrenalectomy the temperature of the brain rose 0.37° C. during asphyxia. Autopsy, however, showed that one-third of the right adrenal was *in situ*. In none of these experiments was any alteration in the temperature of the liver observed, excepting in the animals which had received a preliminary dose of strychnin in which the temperature of the liver fell during the period of asphyxia.

CONCLUSION

Asphyxia produces an increased output of epinephrin which is manifested by an increase in the temperature of the brain.

References

(1) Cannon and Hoskins: *Am. J. Physiol.*, 1911, xxix, 275.
(2) Cannon: Bodily Changes in Pain, Hunger, Fear and Rage, 1915, p. 206.

A COMPARISON OF THE EFFECTS OF THE INJECTION OF GUM ACACIA SOLUTION AND OF THE TRANSFUSION OF BLOOD ON THE OXIDATIVE POWER OF THE BRAIN AS INDICATED BY ALTERATIONS IN TEMPERATURE AFTER THE INJECTION OF ADRENALIN

By George W. Crile, Amy F. Rowland and S. W. Wallace

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In the biophysics laboratory of the Cleveland Clinic it has been shown that adrenalin exercises a specific effect on the oxidative power of the brain, which is manifested in normal animals by an increased temperature of the brain in direct relation to the amount of adrenalin injected.[1] The establishment of this specific effect of adrenalin on the brain has provided us with a criterion whereby to test the capacity of certain agencies for increasing or diminishing the oxidative power of the brain—that is, one would expect that if the oxidative power of the brain is increased by the agent which is being tested, then the response of the brain to an injection of adrenalin given within the period of activity of the agent would be increased. Conversely, the response of the brain to the injection of adrenalin would be diminished in the presence of an agent which depresses the oxidative power of the brain.

In view of the variance of opinion regarding the value of gum acacia (Bayliss) solution as a means of conserving the failing energies of the organism after hemorrhage or after shock, and believing that failing powers presuppose among other things a diminished power of work, hence of oxidation within the brain, it seemed desirable to make a comparative study of the effects of gum acacia solution and of transfusion upon the power of the brain to respond to adrenalin. A six per cent gum acacia solution was used, prepared according to the formula of Bayliss,[2] the solution being used at a temperature of 38.75° C.

These experiments were performed on healthy Belgian hares

[1] *Am. Jour. Physiol.*, 1922, lxii, 370-382; *Proc. Am. Phil. Soc.*, 1922, lxi, 237-245.

[2] Bayliss, W. M., *The Medical Bulletin*, Paris, 1918, No. 6, p. 462.

of from five to seven pounds. From 30 to 50 cc. of blood was withdrawn from each, the quantity in each case being determined by the clinical condition of the animal. None was reduced to extreme prostration. The temperature variations in the brain and the liver were measured by especially constructed thermocouples.

When the maximum effect of the hemorrhage had been produced, as registered by the cessation of the fall in temperature of the brain, four of the animals were given an intravenous infusion of the gum acacia solution, the remaining four receiving a transfusion of citrated blood taken from another rabbit. Table 1 shows the variations in temperature in each of these animals. The significant columns are those which show the maximum temperature attained after the injection of adrenalin as compared (a) with the temperature before the hemorrhage and (b) with the maximum temperature attained after the infusion or transfusion. In every animal which received the transfusion of blood the temperature after the injection of adrenalin rose to a level of from one to nearly two degrees above the temperature of the animal before it was subjected to the hemorrhage. On the other hand, in only one of the three which received the gum acacia solution did the temperature after the adrenalin injection rise even to its level before the hemorrhage. In no instance after the gum acacia infusion was the adrenalin able to raise the temperature of the brain to the maximum attained after the infusion, while in every animal which received the transfusion the maximum rise after the transfusion was surpassed after the injection of adrenalin.

Another significant feature is the length of time after the infusion or transfusion of blood was given, during which the temperature of the brain continued to rise. The longest period of rise after the gum acacia infusion was 14 minutes. On the other hand, the *shortest* period of rise after the transfusion of blood was 1 hour and 23 minutes, the *longest* 3 hours and 52 minutes. The clinical symptoms of the animals throughout corresponded to the temperature observations. In all four of the animals subjected to the gum acacia solution the temperature of the brain fell to a very low level before the termination of the experiment, and the animals were practically *in extremis*. Of the four animals subjected to blood transfusion, all were in good condition at the end of the experiment, and the temperature of each was but little below that at the beginning of the experiment.

TABLE 1

Comparison of the effects of gum acacia (Bayliss) solution and of transfusion of blood on the response of the brain to adrenalin

I. *Gum Acacia*

EXPER. NO.	WT. OF RABBIT	AMOUNT OF HEMORRHAGE	AMOUNT OF INFUSION OR TRANSFUSION	FALL IN T. OF BRAIN DUE TO HEMORRHAGE	TOTAL RISE IN T. OF BRAIN AFTER INFUSION OR TRANSFUSION	PERIOD OF RISE	RISE AFTER ADRENALIN	PERIOD OF SUSTAINED RISE AFTER ADRENALIN	MAX. T. AFTER ADRENALIN AS COMPARED WITH T. BEFORE HEMORRHAGE	MAX. T. AFTER ADRENALIN AS COMPARED WITH MAX. T. AFTER INFUSION OR TRANSFUSION	PERIOD OF SUSTAINED MAXIMUM RISE	
1	6 lbs.	35 cc.	40 cc.	—0.68° C.	+0.52° C.	7½ min.	0.16° C.	2 min.	—0.17° C.	—0.05° C.	30 sec.	
2	5 lbs.	30 cc.	35 cc.	—0.32° C.	+0.68° C.	14 min.	0.45° C. (See Note 1)	0 min.	+0.04° C.	—0.31° C.	0 min.	
3	5½ lbs.	35 cc.	45 cc.	—0.5° C.	Fall —0.21° C.	(net) 1½ min. (See Note 2)	0.25° C.	0 min.	—0.84° C.	—0.09° C.	30 sec.	
4	4½ lbs.	25 cc.	35 cc.	—0.7° C.	Fall —0.8° C.	10 min.	0.1° C.	0 min.	—0.45° C.	—0.17° C.	0 min.	

5	7 lbs.	50 cc.	60 cc.	—0.94° C.	+2.66° C.	3 hrs., 52 min.	0.28° C.	0 min.	+1.12° C.	+0.25° C.	9 min.	Still sustained when adrenalin was given.
6	6⅓ lbs.	40 cc.	45 cc.	—0.48° C.	+1.09° C.	2 hrs., 1 min.	Dose I 0.73° C. Dose II 0.45° C.	Dose I 1 min. Dose II 10 min.	Dose I +1.09° C. Dose II —0.49° C.	Dose I +0.13° C. Dose II + 0.4° C.	0 min.	
7	6 lbs.	35 cc.	40 cc.	—0.41° C.	+1.83° C.	3 hrs., 37 min.	0.17° C.	11 min.	+1.41° C.	+0.11° C.	12 min.	Still sustained when adrenalin was given.
8	6½ lbs.	40 cc.	50 cc.	—1.15° C.	+2.18° C.	1 hr., 23 min.	0.84° C.	3 min.	+1.94° C.	+ 0.39° C.	2 min.	
9	5 lbs.	35 cc.	40 cc.	—0.9° C.	+1.65° C.	1 hr., 16 min.	0.25° C.	(See Note 3)			25 min.	Still sustained when adrenalin was given.

Note 1.—In experiment 2 the adrenalin was given 55 minutes after the maximum rise in temperature when the temperature had fallen 0.76° below the maximum. In all other experiments the adrenalin was injected just as the temperature began to fall after the maximum had been reached.

Note 2.—In experiment 3 the temperature fell 0.6° C. during the infusion and continued to fall for a period thereafter—making the *net* period of rise only 1½ minutes.

Note 3.—Thermocouple broke while temperature of brain was still rising after adrenalin injection.

CONCLUSION

A comparison of the response of the brain to the injection of gum acacia solution and to the transfusion of whole blood indicates that the oxidative power of the brain is markedly diminished by the gum acacia solution, while it is increased by the transfusion of whole blood.

A MATHEMATICAL TREATMENT OF THE ELECTRICAL CONDUCTIVITY OF COLLOIDS AND CELL SUSPENSIONS

By Hugo Fricke

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Many extensive investigations have been made for the purpose of determining the electrical conductivity of cell suspensions such as blood, body tissues, bacterial suspensions, and the like; the biological importance of this constant being that it would give some idea of the permeability of the cells (or the cell walls) in question. The investigations of the conductivity of blood by Bugarszky and Tangl,[1] Fraenckel,[2] Oker-Blom,[3] Roth,[4] Stewart,[5] and others are well known. These investigators found that the

[1] Bugarszky, S., and Tangl, F., Eine Methode zur Bestimmung des relativen Volums der Blutkörperchen und des Plasmas, *Zentr. Physiol.*, 1897–98, xi, 297.

[2] Fraenckel, P., Ueber die Bestimmung des Blutkörperchenvolumens aus der elektrischen Leitfähigkeit, *Z. klin. Med.*, 1904, lii, 470.

[3] Oker-Blom, M., Thierische Säfte und Gewebe in physikalisch-chemischer Beziehung, *Arch. ges. Physiol.*, 1900, lxxix, 510.

[4] Roth, W., Elektrische Leitfähigkeit thierischer Flüssigkeiten, *Zentr. Physiol.*, 1897–98, xi, 271.

[5] Stewart, G. N., The behaviour of the hemoglobin and electrolytes of the coloured corpuscles when blood is laked. *J. Physiol.*, 1899, xxiv, 211. The relative volume of weight of corpuscles and plasma in blood, *ibid.*, 356. The mechanism of hemolysis with special reference to the relations of electrolytes to cells, *J. Pharmacol. and Exp. Therap.*, 1909–10, i, 49.

red corpuscles act as perfect insulators,[6] so that the electric current exclusively passes in the space between them. Oker-Blom, for instance, showed that the resistance of a blood cell suspension of a certain volume concentration was equal to the resistance of a suspension of quartz sand of equal volume concentration in the same suspending medium. The ratio of the resistance of the blood suspension to the resistance of the suspending medium in this case is, therefore, a function of the volume concentration of the corpuscles alone. Experience shows that this function is independent of the size and only slightly dependent on the shape of the suspended particles. In the case of suspensions of cells such as bacteria, part of the current generally goes through the intercellular liquid and part goes through the cells. The resulting conductivity of the suspension is, therefore, a function both of the specific conductivity of the suspending medium and of the specific conductivity of the cellular substance as well as of the volume concentration.

The purpose of the present paper is to derive a formula whereby the specific conductivity of the cellular substance may be calculated from observed values of the specific conductivity of suspensions of the cells in question and of the suspending medium. This formula will be here derived for the simple case of a dilute suspension of spherical homogeneous cells. Nevertheless, the formula can be applied also with fair accuracy to the more general case of a suspension of homogeneous ellipsoids, for it is found that up to a quite large value for the eccentricity of the ellipsoids the same formula as that for homogeneous spheres is applicable. This is in accord with the findings of Oker-Blom and Fraenckel mentioned above, that the conductivity of suspensions of red corpuscles and of quartz sand depends only on the volume concentration of the suspensions.

It may be well at this point to consider briefly the assumption that the cells are homogeneous. In general, a single cell comprises many regions of varying conductivities, as indicated, for instance, by the very large polarization capacity of all living cells. Thus, it is probable that all cells are surrounded by a thin membrane which is semipermeable and in consequence has a comparatively high resistance. However, the formula applicable to a cell consisting of several concentric layers of different conductivities will be identical with that which we shall develop for a homo-

[6] It is to be understood that this apparently high resistance to an electric current of low frequency may be wholly due to polarization at the surfaces of the red corpuscles.

geneous sphere, the specific conductivity of the homogeneous sphere being replaced by a certain average value of the conductivities of the different layers of the non-homogeneous cell.[7]

We shall, therefore, consider the case of a suspension of homogeneous spheres (radius a, specific conductivity of cell material k_1) in a medium of specific conductivity k_2. We shall assume that the suspension is so diluted that each sphere acts as if it were alone in the suspending medium—that is, that the spheres are so far apart that the current lines become parallel in the space between them. As will be shown below, a comparison with experimental data shows that within an accuracy of a few per cent this assumption is fulfilled with concentrations from zero up to 30 per cent.

Let us consider first the case of a single sphere suspended in the medium. We assume that the medium is placed in an electrolytic cell with a volume of 1 cc. and that a constant electrical current, i, passes through the suspension. The difference in potential of the electrodes we shall designate as V. Since the electrodes are 1 cm. apart, V is equal to the electric force. The surface of the sphere is the seat of a certain distribution of surface charges. The surface charge, S, at an arbitrary point can be developed into a series of surface harmonics.[8]

$$S = \alpha_0 S_0 + \alpha_1 S_1 + \alpha_2 S_2 + \ldots\ldots \alpha_n S_n + \ldots\ldots = \Sigma \alpha_n S_n.$$

The potential at any point outside the sphere is[9]

$$V_{\text{ext.}} = 4\pi \Sigma \frac{a^{n+2} \cdot \alpha_n \cdot S_n}{(2n+1) r^{n+1}} \tag{1}$$

r being the distance of the point from the center of the sphere. The potential at an internal point is

$$V_{\text{int.}} = 4\pi \Sigma \frac{r^n \cdot \alpha_n \cdot S_n}{(2n+1) a^{n-1}} \tag{2}$$

The component of the electric force perpendicular to the surface at a point situated on the external surface of the sphere is

$$F_{r_{\text{ext.}}} = -\frac{dV_{\text{ext.}}}{dr_{(r=a)}} = 4\pi \Sigma \frac{n+1}{2n+1} \cdot \alpha_n \cdot S_n$$

[7] The treatment of the general case of an ellipsoid having a surface layer of a conductivity different from that of its interior will be taken up in a paper which will appear in the *Physical Review*. This case includes that of a homogeneous polarizable ellipsoid.

[8] See Jeans, J. H., The mathematical theory of electricity and magnetism, Cambridge, 1920, p. 206.

[9] Jeans,[8] p. 224.

At a point situated on the internal surface of the sphere we have for the same component:

$$F_{r_{\text{int.}}} = -\frac{dV_{\text{int.}}}{dr_{(r=a)}} = -4\pi\Sigma\frac{n}{2n+1}\alpha_n \cdot S_n.$$

These forces are the forces due to the electric charges on the spheres. The total forces are obtained by adding the component of the original electric force due to the surface charges on the electrodes of the electrolytic cell. This component is equal to $-V\sin\varphi$.

The electric force has a discontinuity at the surface of the sphere. At the moment when the current through the suspension is started, the electric force is the same on the two opposite sides of the surface of the sphere. As soon as the current is started, since the conductivity of the substance of the sphere is different from the conductivity of the suspending medium, a different amount of electricity will be carried to the outside of an element of surface from that which is being carried away from the inside at the same instant. Thus, an accumulation of charge on the surface begins and is continued until the difference between the electric forces on the two sides of the surfaces of the sphere becomes so large that the same amount of electricity is carried to the outside of the surface as is carried away from the inside in the same time interval. That is, the equation of equilibrium is

$$\left(F_{r_{\text{ext.}}} - V\sin\varphi\right)k_1 = \left(F_{r_{\text{int.}}} - V\sin\varphi\right)k_2$$

or

$$\left(4\pi\Sigma\frac{n+1}{2n+1}\alpha_n S_n - V\sin\varphi\right)k_1 = \left(-4\pi\Sigma\frac{n}{2n+1}\alpha_n S_n - V\sin\varphi\right)k_2 \qquad (3)$$

We have [9]

$$S_0 = 1$$
$$S_1 = \sin\varphi$$
$$S_2 = \tfrac{1}{2}(3\sin\varphi^2 - 1)$$

In order that the right and the left side of equation (3) be identities it is necessary that α_n be made zero for all values of n except 1. Consequently equation (3) reduces to

$$(4\pi\cdot\tfrac{2}{3}\alpha_1\sin\varphi - V\sin\varphi)k_1 = (-4\pi\cdot\tfrac{1}{3}\alpha_1\sin\varphi - V\sin\varphi)k_2$$

from which we derive the value of α_1.

$$\alpha_1 = \frac{V\,(k_1 - k_2)}{\frac{4\pi}{3}\,(2k_1 + k_2)}$$

Substituting this value for α_1, in equations (1) and (2) for the potentials $V_{\text{ext.}}$ and $V_{\text{int.}}$ we now obtain

$$V_{\substack{\text{ext.}\\ r=a}}(\varphi) = a \cdot \frac{V\,(k_1 - k_2)}{(2k_1 + k_2)} \sin\varphi$$

$$V_{\substack{\text{int.}\\ r=a}}(\varphi) = a \cdot \frac{V\,(k_1 - k_2)}{(2k_1 + k_2)} \sin\varphi$$

The conductivity of the suspension can now be calculated by means of the following method. The space between the electrodes of the electrolytic cell is divided into an infinite number of volume elements, dS, dx; dS being a surface element parallel to the electrodes and dx a line element perpendicular to the electrodes. If F_x is the component of the electric force along x then by using Ohm's law

$$\iint F_x \cdot dS \cdot dx \cdot k_1 + \iint F_x \cdot dS \cdot dx \cdot k_2 = \int i dx = V \cdot k \quad (4)$$

k being the conductivity of the suspension. The first integration is taken over all volume elements outside the sphere, the second integration over all elements inside the sphere.

In carrying through this integration on the left side we integrate all elements situated in the cylinder defined by a fixed dS. If this cylinder does not cross the sphere, its elements contribute solely to the first integral. This contribution is

$$\text{Contr.}_1 = \iint F_x\, dS \cdot dx\, k_1 = \int k_1\, dS \cdot \int F_x\, dx = k_1\, V \cdot \int dS = k_1\, V \cdot (1 - \pi a^2).$$

The contribution of the cylinders crossing the sphere to the left side of our equation is

$$\text{Contr.}_2 = \iint F_x\, dS\, dx\, k_1 + \iint F_x\, dS\, dx\, k_2 = \int (V - \Delta V)\, dS\, k_1 + \int \Delta V\, dS\, k_2$$

ΔV being the difference in potential between the two points, P_1 and P_2, where the cylinder crosses the surface of the sphere. Then, according to what was found above

$$\Delta V = V_{\substack{\text{int.} \\ r=a}}(\varphi) - V_{\substack{\text{int.} \\ r=a}}(-\varphi) + 2\,Va\sin\varphi$$

$$= 2 \cdot V\frac{(k_1 - k_2)}{2\,k_1 + k_2} a \sin\varphi + 2\,Va\sin\varphi$$

$$= 2\,Va \cdot \frac{3\,k_1}{2\,k_1 + k_2}\sin\varphi.$$

Consequently taking

$$dS = 2\,\pi\,a\cos\varphi\,d\,(a\cos\varphi)$$
$$= 2\,\pi\,a^2\cos\varphi\,d\,(\cos\varphi)$$

$$\text{Contr.}_2 = \int V\,dS \cdot k_1 + \int_{\frac{\pi}{2}}^{0} \Delta V\,(k_2 - k_1)\,2\,\pi\,a^2\cos\varphi\,d\,(\cos\varphi)$$

$$= \pi a^2\,V\,k_1 + \int_{\frac{\pi}{2}}^{0} 2\,Va \cdot \frac{3\,k_1}{2\,k_1 + k_2}\sin\varphi\,(k_2 - k_1)$$
$$2\,\pi\,a^2\cos\varphi\,d\,(\cos\varphi).$$

$$= \pi a^2\,V\,k_1 + \frac{12\,\pi\,k_1\,(k_2 - k_1)}{2\,k_1 + k_2}\,Va^3 \int_{\varphi=0}^{\varphi=\frac{\pi}{2}} \sin^2\varphi\,d\,(\sin\varphi)$$

$$= \pi a^2\,V\,k_1\left(1 + \frac{4\,(k_2 - k_1)}{2\,k_1 + k_2}\,a\right).$$

Using the expressions obtained for Contr._1 and Contr._2 equation (4) becomes

$$V\,(1 - \pi\,a^2)\,k_1 + \pi\,a^2\,V\,k_1\left(1 + \frac{4\,(k_2 - k_1)}{2\,k_1 + k_2}\,a\right) = Vk$$

$$Vk_1 + \frac{4\,(k_2 - k_1)}{2\,k_1 + k_2}\pi\,a^3\,Vk_1 = Vk$$

$$k = k_1 + \frac{4\,(k_2 - k_1)}{2\,k_1 + k_2}\,\pi\,a^3\,k_1.$$

Calling the volume of the sphere ρ we obtain

$$k = \left(1 + \frac{3\,(k_2 - k_1)}{2\,k_1 - k_2}\,\rho\right) k_1$$

or

$$\frac{k}{k_1} = 1 + \frac{3\left(1 - \frac{k_1}{k_2}\right)}{1 + 2\frac{k_1}{k_2}} \cdot \rho \qquad (5)$$

This formula with ρ being the total volume of spheres per cc. will hold for a suspension of spheres so diluted that each sphere deforms the current lines of the original current independently of every other.

We see that $\frac{k}{k_1}$ is a linear function of ρ.

From equation (5) we derive the value for $\frac{k_2}{k_1}$

$$\frac{k_2}{k_1} = \frac{1 + 2\,\frac{\frac{k}{k_1} - 1}{3\,\rho}}{1 - \frac{\frac{k}{k_1} - 1}{3\,\rho}} \qquad (6)$$

The above formula shows that for diluted cell suspensions $\frac{\frac{k}{k_1} - 1}{3\rho}$ is independent of the concentration.

A test of the theory here developed has been made by applying formula (6) to red corpuscles. As was stated above, red corpuscles are very nearly non-conductors; that is, $k_2 = 0$. According to our theory $\frac{\frac{k}{k_1} - 1}{3\rho}$ should therefore have the constant value of $-\frac{1}{2}$.

In Table I are given the values of $\frac{\frac{k}{k_1} - 1}{3\rho}$ calculated from data given by Fraenckel for red corpuscles of man, dog, horse, and cow. It is seen that the experimental value of $\frac{\frac{k}{k_1} - 1}{3\rho}$ has the theoretical

TABLE I

$\frac{\frac{k}{k_1}-1}{\beta}$	ρ
	per cent
—0.53	10
—0.52	20
—0.50	30
—0.47	40
—0.44	50

value of —0.50 up to concentrations of between 30 and 40 per cent. The formula here developed can therefore be expected to hold up to this limit of concentration.

Experiments dealing with the applications of the theory here developed to colloids (especially graphite suspensions) and to suspensions of different living cells are at present being made in this laboratory and will be reported in a later paper.

THE ELECTRIC CONDUCTIVITY OF DISPERSE SYSTEMS.

By Hugo Fricke

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From the *Journal of General Physiology*, Vol. vi, No. 6, July 20, 1924, pp. 741-746.

In another paper, p. 341, I have presented a theory for the conductivity of a suspension of homogeneous spheroids [1] in which the following formula was derived.

$$\frac{k-k_1}{k-k_2}\left(1-\frac{k_2}{k_1}\right)=\beta\cdot\frac{\rho}{1-\rho} \qquad (1)$$

k, specific conductivity of suspension.
k_1, " " " suspending medium.
k_2, " " " suspended medium.
ρ, volume concentration " " "

[1] The theory for the simple case of a diluted suspension of spheres is given in the paper on p. 341.

$$\beta = \frac{1}{3}\left[\frac{2}{1+\left(\frac{k_2}{k_1}-1\right)\int_0^\infty \frac{d\lambda}{\left(1+\frac{b^2}{a^2}\lambda\right)^{\frac{1}{2}}\left(1+\lambda\right)^2}} + \frac{1}{1+\left(\frac{k_2}{k_1}-1\right)\left(1-\int_0^\infty \frac{d\lambda}{\left(1+\frac{b^2}{a^2}\lambda\right)^{\frac{1}{2}}\left(1+\lambda\right)^2}\right)}\right]\left(\frac{k_2}{k_1}-1\right)$$

a, b, axes of spheroid.

For the case of the sphere $\left(\frac{a}{b}=1\right)$, formula (1) reads [1]

$$\frac{\frac{k}{k_1}-1}{\frac{k}{k_1}+2} = \rho\,\frac{\frac{k_2}{k_1}-1}{\frac{k_2}{k_1}+2} \tag{2}$$

For a diluted solution $\frac{k}{k_1}$ is approximately equal to 1; introducing this value of $\frac{k}{k_1}$, equation (2) reduces to

$$\frac{k}{k_1} = 1 + 3\rho\,\frac{\frac{k_2}{k_1}-1}{\frac{k_2}{k_1}+2} \tag{3}$$

This is the equation, the derivation of which was given in another paper.[1]

It is of interest to note that according to equation (1), for a constant volume concentration of the suspended medium the conductivity of a suspension is independent of the size of the suspended particles and also nearly independent of the form of the particles when the difference between the conductivities of the suspended and the suspending media is not very large. This is especially true for suspensions of prolated spheroids which are less conductive than the suspending medium.

Investigations in which formula (1) is being applied to different problems of practical and theoretical interest are at present being made in this laboratory. In the first of these studies which will

[1] The theory for the simple case of a diluted suspension of spheres is given in the paper on p. 341.

be published shortly, the case of cream will be considered. In the present paper the formula will be applied to the case of blood.

The most exact investigations of the conductivity of blood in terms of the volume concentration of the red corpuscles have been made by Stewart [2] and Fraenckel.[3] Stewart has determined the volume concentration by two independent methods, a colorimetric method and the Hoppe-Seyler chemical method. Fraenckel has used Bleibtreu's chemical method. The agreement between the results secured by these investigations is very close. However, as has been stated also by Fraenckel, one would expect that Stewart's methods would give the most exact results and therefore we shall here consider only his measurements. In Table 1 is given a series

TABLE 1

Conductivity of Blood of Dog

$\frac{k_1}{k}$	ρ observed *per cent*	ρ calculated *per cent*	Δ *per cent*
15.62	90.7	88.4	+ 2.6
9.08	82.1	80.9	+ 1.5
6.56	74.5	74.4	+ 0.1
5.06	67.8	68.0	— 0.3
4.14	61.6	62.1	— 0.8
3.51	56.1	56.8	— 1.2
3.063	51.0	51.9	— 1.8
2.726	46.4	47.4	— 2.2
2.436	42.2	42.9	— 1.6
2.348	41.0	41.3	—0.7
2.225	38.4	39.0	— 1.6
1.903	31.9	32.0	— 0.3
1.697	26.4	26.7	— 1.1
1.539	21.8	22.0	— 0.9
1.428	18.1	18.3	— 1.1
1.342	15.3	15.2	+ 0.7
1.232	11.4	10.8	+ 5.5

of measurements made by Stewart [4] for the blood of a dog. The volume concentration of the normal blood was determined twice by the colorimetric method and twice by the Hoppe-Seyler method. The results were as follows: 41.16, 40.72, 41.52, and 40.99 per cent, the average being 40.98 per cent. A series of red corpuscle suspensions of varying volume concentration was made by concentration or dilution of the normal blood. The volume concen-

[2] Stewart, G. N., *J. Physiol.*, 1899, xxiv, 356.
[3] Fraenckel, P., *Z. klin. Med.*, 1904, lii, 470.
[4] Stewart,[2] p. 369.

tration for each of these suspensions was determined volumetrically using the value of the volume concentration of the original blood. The volume concentrations are given in Table I under ρ observed. The ratio of the observed conductivity of the serum to that of the blood is given under $\frac{k_1}{k}$. In order to employ formula (1) we consider $\frac{a}{b} = \frac{1}{4}$; consequently $\beta = -1.91$. Furthermore, $k_2 = 0$. The formula therefore reads

$$1 - \frac{k_1}{k} = -1.91 \cdot \frac{\rho}{1 - \rho}$$

The values of the volume concentration ρ calculated from this formula using the observed values of $\frac{k_1}{k}$ are given under ρ calculated. The percentile differences between ρ observed and ρ calculated are given under Δ. The deviations throughout are within the limits of experimental errors.

Before concluding, it may perhaps be of interest to apply our formula to some measurements of sand suspensions which have been made by Oker-Blom [5] and which often are cited in connection with investigations of the conductivity of blood. Two different kinds of sand were used in these investigations. The suspensions were prepared by adding the sand to a hot salt solution containing 3 per cent gelatin and cooling this mixture to gelatination under continuous rotation. No information is given concerning the form of the sand particles except for the statement that the particles of the sand which were used in the second series of experiments

TABLE 2

Conductivity of Suspensions of Sand.

$\frac{k_1}{k}$ observed	ρ observed *per cent*	β
2.488	40.0	2.22
2.220	36.4	2.14
2.075	33.3	2.15
1.952	30.8	2.14
1.866	28.6	2.17
1.790	26.7	2.17
1.725	25.0	2.18
1.6835	23.5	2.22

Average value of β, 2.17.

[5] Oker-Blom, M., *Arch. ges. Physiol.*, 1900, lxxix, 510.

TABLE 3

Conductivity of Suspensions of Sand.

$\frac{k_1}{k}$ observed	ρ observed *per cent*	β
1.190	10	1.710
1.426	20	1.705
1.734	30	1.712
2.156	40	1.732
2.715	50	1.715
3.613	60	1.74

Average value of β, 1.72.

(Table 3) were more nearly spherical than those which were used in the first series (Table 2). Our theory is therefore best applied by using Oker-Blom's observed values of $\frac{k_1}{k}$ and ρ and calculating the value of β by means of the formula $1 - \frac{k_1}{k} = -\beta \cdot \frac{\rho}{1-\rho}$ obtained from formula (1) by considering $k_2 = 0$. Our calculated results are given in Tables II and III, the sand used in the measurements in the two tables corresponding to the two kinds of sand used by Oker-Blom. The calculated values for β are constant within experimental errors. The deviation of the value of β from 1.50 is a measure of the deviation of the sand particles from the spherical form.

A MATHEMATICAL TREATMENT OF THE ELECTRIC CONDUCTIVITY AND CAPACITY OF DISPERSE SYSTEMS

I. The Electric Conductivity of a Suspension of Homogeneous Spheroids

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A. Introduction

The present theory has been developed as a basis for experiments concerning the electric conductivity and capacity * of colloids and

* A suspension is electrically equivalent to a certain resistance in parallel with a certain capacity. We refer to this resistance and to this capacity when we speak of the conductivity and capacity of a suspension.

biological cell suspensions, like blood for instance, which for sometime have been carried out in this laboratory. In this paper we shall consider the electric conductivity of a suspension of homogeneous non-polarizable spheroids; in a second paper, the electric capacity of a suspension of polarizable homogeneous spheroids for a current of low frequency; and in a third, the conductivity and capacity for any frequency, of a suspension of spheroids each consisting of a homogeneous interior surrounded by a thin membrane, the conductivity of which is different from the conductivity of the interior. The last calculation includes the case of a suspension of homogeneous polarizable spheroids. A series of measurements illustrating the practical and theoretical applicability of the theory will be given in separate papers. Preliminary reports of some of the measurements have already been presented at meetings of the American Physical Society.

An investigation of the conductivity of a suspension may serve as a means of determining the conductivity of the single particles of the suspension. Important knowledge of the state of the suspended particles may thus be obtained, as in the case of protected metallic colloids, and especially in the case of suspensions of biological cells the life of which seems to be associated with the existence of a characteristic semi-permeability of the exterior cell wall and of the different interphases of the cell interior. In connection with the latter case we may refer to the researches of Brooks,[1] of Crile, Hosmer and Rowland,[2] of Osterhout[3] and of many other investigators on the changes of the electric conductivity of bacterial suspensions and of different plant and animal tissues under varying conditions.

The determination of the conductivity of a suspension may also furnish a method for obtaining the volume concentration of the suspension when the specific conductivity of the disperse phase and of the suspending medium is known. This method is used practically in the determination of the volume concentration of the red corpuscles of blood. It seems probable that it may have many other practical applications, as for instance, the determination of the butter-fat of cream.

Finally, the measurement of the conductivity of a suspension

[1] J. Brooks, *J. Gen. Physiol.* 5, 365 (1923); *Proc. Soc. Exp. Biol. and Med.*, 19, 284 (1922).

[2] G. W. Crile, H. R. Hosmer, and A. F. Rowland, *Amer. J. Physiol.*, 60, 59 (1922).

[3] W. J. V. Osterhout, Injury, Recovery and Death in Relation to Conductivity and Permeability, Phila., 1922.

may lead to a determination of the structural factors of the suspended phase. This is possible because as we shall see later, for a constant volume concentration the conductivity of a suspension is to a certain extent dependent on the form (but not on the size) of the suspended particles. This is especially marked when the suspended particles are non-conductors, the condition which is of the most practical interest. This method may, for instance, find practical application in soil analysis.

B. Theory of Electric Conductivity of Suspension of Spheroids

The determination of the electric conductivity of a suspension belongs to a very important group of physical problems all of which depend on the solution of Poisson's equation for a two-phase system, including Poisson's theory of induced magnetism, the Clausius-Mossotti theory for the dielectric constant, the Lorenz-Lorentz theory for the index of refraction, etc. Applied to the case of electric conductivity, the formula to which these theories lead, reads

$$\frac{(k/k_1) - 1}{(k/k_1) + 2} = \rho \frac{(k_2/k_1) - 1}{(k_2/k_1) + 2} \tag{1}$$

in which k, k_1 and k_2 are the specific conductivities of the suspension, the suspending and the suspended mediums respectively; and ρ is the volume concentration of the suspended medium. This formula is true theoretically only for the case of a suspension of spheres. The case of a suspension of infinitely well conducting ellipsoids has been treated theoretically by Poisson [4] in his theory of magnetic induction and also by Lampa [5] in his theory of the dielectric constant of a crystal.

According to its theoretical derivation as presented hitherto, Eq. (1) can be expected to hold only for dilute suspensions. The reason for this is that in the given theoretical treatment the electric field around any suspended particle due to the electric charges on the other particles in the suspension is considered as equal to the average value of this field over the whole space of the suspended medium. For the case of a cubic arrangement of spheres, Lord Rayleigh [6] has shown that the influence of these charges is repre-

[4] S. D. Poisson, *Mem. Acad. Roy. Sci. Inst.*, France, 5, 488 (1826).
[5] A. Lampa, *Sitz, Math. Nat. Klasse Akad. Wiss.*, Wien., 104 (IIa), 681 (1895).
[6] Lord Rayleigh, *Phil. Mag.*, 34, 481 (1892).

sented correctly in Eq. (1) only to the first approximation. It seems difficult theoretically to decide whether the formula holds strictly for the case of a random distribution of the suspended particles. That it does is supported by the well-known fact that there is usually a very close agreement[7] between the values of the refractive index of a liquid (or dielectric constant, although the agreement here generally is less close)[8] as determined experimentally and as calculated from formula (1) by means of the experimental value of the refractive index for its vapor. Confirmation was obtained for volume concentrations up to 15 per cent by Millikan[9] from his observations of the dielectric constant of emulsions of water in benzol-chloroform. In the following presentation, therefore, we shall take into account the interaction of the suspended particles by means of the procedure employed in deriving formula (1); that is, we shall add to the original field the mean value of the forces due to the charges on the suspended particles throughout the whole space of the suspending medium. The exactness of this method is proven by an experimental verification of the formula which we shall derive; to this end we shall in this paper make use of the extensive experimental data which have been accumulated for the electric conductivity of blood.

We shall consider first the general case of a suspension of homogeneous, non-polarizable ellipsoids. The suspension is assumed to be in an electrolytic cell, the dimensions of which are $1 \times 1 \times 1$ cm. The potential between the electrodes is V volts; the current i amperes.

Let us consider a single ellipsoid with half axes a, b, c in this suspension. We shall, for the moment, consider a to be parallel to the direction of the electric force. We shall introduce an orthogonal coördinate system with its origin in the center O of the ellipsoid and its axes x, y, z parallel to a, b and c. We shall designate the electric force at an arbitrary point of the suspending phase as F; as stated above, this is composed of the original electric force V due to the surface charges on the electrodes and of the mean value of the forces due to the surface charges on the suspended particles throughout the whole space of the suspending medium.

For the purpose of determining the surface charges of the ellipsoid we shall introduce confocal coördinates defining these for a

[7] W. Brühl, *Zeits. Phys. Chem.*, 7, 1 (1891).
[8] P. Lebedew, *Wied. Ann.*, 44, 304 (1891).
[9] R. A. Millikan, *Wied. Ann.*, 61, 337 (1897).

point x, y, z as the three values of θ, λ, μ and ν, which satisfy the equation

$$\frac{x^2}{a^2+\theta}+\frac{y^2}{b^2+\theta}+\frac{z^2}{c^2+\theta}=1.$$

The potential due to the force F is

$$V_x=-Fx=-F\sqrt{(a^2+\lambda)\,(a^2+\mu)\,(a^2+\nu)/\,(b^2-a^2)\,(c^2-a^2)}.$$

The total potential at a point outside the ellipsoid must be of the form

$$V_{ext}=-F\sqrt{\frac{(a^2+\mu)\;(a^2+\nu)}{(b^2-a^2)\;(c^2-a^2)}}\left\{\sqrt{(a^2+\lambda)}+D\sqrt{(a^2+\lambda)}\int_{\lambda}^{\infty}\frac{d\lambda}{(a^2+\lambda)\,\Delta\lambda}\right\} \tag{2}$$

while at a point inside the ellipsoid

$$V_{int}=-F\sqrt{\frac{(a^2+\lambda)\;(a^2+\mu)\;(a^2+\nu)}{(b^2-a^2)\;(c^2-a^2)}}D_1 \tag{3}$$

where $\Delta\lambda=\sqrt{(a^2+\lambda)\;(b^2+\lambda)\;(c^2+\lambda)}$, and D and D_1 are constants which are to be determined by the boundary conditions. The boundary conditions to be fulfilled are

(1) For $\lambda=\infty$, V_{ext} must be equal to the potential of the original field; this condition is fulfilled since the last term becomes zero for $\lambda=\infty$.

(2) At the surface of the ellipsoid ($\lambda=0$), $V_{int}=V_{ext}$; hence, from Eqs. (2) and (3),

$$D_1=1+D\int_{0}^{\infty}\frac{d\lambda}{(a^2+\lambda)\,\Delta\lambda} \tag{4}$$

Hence

$$\int_{0}^{\infty}\frac{d\lambda}{(a^2+\lambda)\,\Delta\lambda}=\frac{D_1-1}{D}\equiv L_a\,,$$

if we write L_a for the definite integral.

At the surface of the ellipsoid, $N_{ext}\,k_1=N_{int}\,k_2$, N_{ext} and N_{int} being the normal forces at the two sides of the surface of the ellipsoid. The equation indicates that no accumulation of electricity takes place at the surface. Using n for the direction of the normal to the surface of the ellipsoid we have

$$N_{ext}=-\,(dV_{ext}/dn)_{\lambda=0}=-\,(dV_{ext}/d\lambda)_{\lambda=0}\cdot(d\lambda/dn)_{\lambda=0}$$

and a similar equation for N_{int}.

Consequently our equation of condition becomes

$$+F\sqrt{\frac{(a^2+\mu)\ (a^2+\nu)}{(b^2-a^2)\ (c^2-a^2)}}\left[\frac{1}{2a}+\frac{DL_a}{2a}-\frac{D}{a^2bc}\right]k_1$$

$$=+F\,D_1\sqrt{\frac{(a^2+\mu)\ (a^2+\nu)}{(b^2-a^2)\ (c^2-a^2)}}\ \frac{1}{2a}k_2:$$

$$k_1[1+DL_a-2D/abc]=k_2D_1. \tag{5}$$

From equations (4) and (5) we obtain:

$$D=\frac{(1-k_2/k_1)}{2/abc+L_a(k_2/k_1-1)}$$

$$D_1=\frac{2}{2+abc\,L_a(k_2/k_1-1)}$$

We now obtain for V_{int}

$$V_{int}=-F\sqrt{\frac{(a^2+\lambda)\ (a^2+\mu)\ (a^2+\nu)}{(b^2-a^2)\ (c^2-a^2)}}\cdot\frac{2}{2+abc\,L_a(k_2/k_1-1)}$$

or, going back to the x, y, z coördinate system

$$V_{int}=-\frac{2\,Fx}{2+abc\,L_a(k_2/k_1-1)}. \tag{6}$$

The values of V_{int} when b or c are parallel to the electric field, are derived by replacing a in Eq. (6) by b or c.

The value of F is determined by the following equation:

$$\int_{ext} F_x\,dx\,dS+\int_{int} F_x\,dx\,dS=V$$

in which F_x is the component of the electric force parallel to x and dS an element of area perpendicular to x; the first integral is taken over the space outside the ellipsoids, the other over the space inside the ellipsoids.

We obtain, using equation (6) and writing

$$\int_0^\infty\frac{d\lambda}{(b^2+\lambda)\ \Delta\lambda}\equiv L_b\ ;\quad\int_0^\infty\frac{d\lambda}{(c^2+\lambda)\ \Delta\lambda}\equiv L_c$$

$$V=F(1-\rho)+\tfrac{1}{3}F\rho\sum^{a=a,b,c}\frac{2}{2+abc\,L_a(k_2/k_1-1)}. \tag{7}$$

In order to find the conductivity k of the suspension we shall divide the space between the electrodes into an infinite number of volume elements dS, dx.

By Ohm's law we have

$$k_1 \int_{int} dx \int_{int} F_x \, dS + k_2 \int_{ext} dx \int_{ext} F_x \, dS = i = Vk \tag{8}$$

where the first of the two integrals is taken over the space inside the ellipsoids and the other over the space outside the ellipsoids. This equation is evidently equivalent to

$$k_1 \int_{all} dx \int_{all} F_x \, dS + (k_2 - k_1) \int_{ext} dx \int_{ext} F_x \, dS = Vk$$

in which the first double integral is taken over the whole space between the electrodes. We obtain

$$Vk_1 + (k_2 - k_1) \int dS[(V_{int})_{-x} - (V_{int})_{+x}] = Vk$$

$$Vk_1 + (k_2 - k_1) \frac{2F}{2 + abc\, L_a(k_2/k_1 - 1)} \int 2x \, dS = Vk$$

$$k_1 + \frac{2k_1(k_2/k_1 - 1)F/V}{2 + abc\, L_a(k_2/k_1 - 1)} \rho = k \tag{9}$$

ρ being the volume of the ellipsoids.

This equation corresponds to the case in which a is parallel to the direction of the original field. The equations which correspond to the cases in which b and c are parallel to the original field are obtained by replacing a by b and c.

The equation corresponding to an arbitrary orientation of the ellipsoids is the sum of three equations like (9)

$$3k_1 + k_1\rho \sum^{a=a,b,c} \frac{2(k_2/k_1 - 1)F/V}{2 + abc\, L_a(k_2/k_1 - 1)} = 3k \tag{10}$$

Combining this equation with equation (7) we obtain

$$\frac{F}{V} = \frac{k_2 - k}{(1 - \rho)(k_2 - k_1)}$$

Introducing this value of F/V into equation (10), we obtain finally

$$k = k_1 + \frac{\frac{1}{3}\rho}{1 - \rho} \sum^{a=a,b,c} \frac{2(k_2 - k)}{2 + abc\, L_a(k_2/k_1 - 1)}. \tag{11}$$

We shall now confine ourselves to the case of spheroids, that is

$b = c$. We have the following two integrals in equation (11) to integrate

$$L_a = \int_0^\infty \frac{d\lambda}{(a^2+\lambda)\,\Delta\lambda} = \int_0^\infty \frac{d\lambda}{(a^2+\lambda)^{3/2}(b^2+\lambda)}$$

$$L_b = \int_0^\infty \frac{d\lambda}{(b^2+\lambda)\,\Delta\lambda} = \int_0^\infty \frac{d\lambda}{(b^2+\lambda)^2(a^2+\lambda)^{1/2}}$$

We find by partial integration

$$L_a = \frac{2}{ab^2} - 2\int_0^\infty \frac{d\lambda}{(a^2+\lambda)^{1/2}(b^2+\lambda)^2}.$$

The integral

$$ab^2\int_0^\infty \frac{d\lambda}{(a^2+\lambda)^{1/2}(b^2+\lambda)^2} \equiv M$$

can easily be calculated.

$M\ (a<b) = \dfrac{(\varphi - \frac{1}{2}\sin 2\varphi)}{\sin^3\varphi}\cos\varphi$ where $\cos\varphi = a/b$, and

$M\ (a>b) = \dfrac{1}{\sin^2\varphi'} - \dfrac{1}{2}\dfrac{\cos^2\varphi'}{\sin^3\varphi'}\log\left(\dfrac{1+\sin\varphi'}{1-\sin\varphi'}\right)$, where

$\cos\varphi' = b/a$ consequently by (11),

$$k = k_1 + \frac{k_1\rho\beta}{(1-\rho)}\frac{(k_2-k)}{(k_2-k_1)} \tag{12}$$

or

$$\left(\frac{k-k_1}{k_2-k}\right)\left(\frac{k_2}{k_1}-1\right) = \frac{\beta\rho}{1-\rho} = \beta\rho_1 \tag{13}$$

where $\rho = \rho_1/(1+\rho_1)$

and

$$\beta = \tfrac{1}{3}\left[\frac{2}{1+(k_2/k_1-1)\frac{1}{2}M} + \frac{1}{1+(k_2/k_1-1)\,(1-M)}\right]\left(\frac{k_2}{k_1}-1\right)$$

The influence of the geometrical factors of the suspended particles is expressed in equation (13) solely in β. Therefore we conclude from the expression for β that for a constant volume concentration, the conductivity of a suspension is independent of

the size of the suspended particles and also nearly independent of the form of the particles when the difference between the conductivities of the suspended and the suspending phases is not very large. This is especially true for suspensions of prolated spheroids which are less conducting than the suspending medium.

Putting

$$x = -\frac{(k_2/k_1 - 1) - (k_2/k_1)\beta}{(k_2/k_1 - 1) - \beta}$$

we obtain from equation (13) the following analogue to equation (1) [10]

$$\frac{(k/k_1) - 1}{(k/k_1) + x} = \rho \cdot \frac{(k_2/k_1) - 1}{(k_2/k_1) + x} \tag{14}$$

For the case of the sphere, $x = 2$, making Eq. (14) identical with Eq. (1).

For the case when $k_2 = 0$, Eq. (13) becomes

$$\left(1 - \frac{k_1}{k}\right) = \frac{\beta\rho}{1 - \rho} = \beta\rho_1 \; ; \tag{15}$$

also

$$x = -1/(\beta + 1) \; ; \; \beta = -(x + 1)/x, \tag{16}$$

and Eq. (14) becomes

$$-\frac{\rho}{x} = \frac{k - k_1}{k + k_1 x} \; ; \quad \left[1 - \frac{k_1}{k}(1 - \rho)\right] x = -\rho \tag{17}$$

C. Comparison of Theory with Experimental Data

In this section we shall apply the formula which we have derived to the very accurate and extensive experimental data for the conductivity of blood which have been accumulated by Stewart,[11] Bugarszky,[12] Fraenckel [13] and others. According to these investigators for a current of low frequency the red corpuscles of blood are perfect insulators so that the ratio of the conductivity of blood to that of its serum is dependent only on the volume concentration of the red corpuscles but independent of the absolute value of the conductivity of the serum. Determinations of this ratio are made for volume concentrations up to 90 per cent. For

[10] Compare O. Wiener, *Abh. K. Sächs. Ges. Wiss. Math. Phys. Kl.* 32, 509 (1912).

[11] G. N. Stewart, *J. Physiol.*, 24, 356 (1899).

[12] S. Bugarszky, *Zentr. Physiol.*, 11, 297 (1897-98).

[13] P. Fraenckel, *Zeits. klin. Med.*, 52, 470 (1904).

the same value of the volume concentration, this ratio is very nearly the same for the blood of man, horse, dog and cow.[13] The most exact methods for determining the volume concentration have been used by Stewart and Fraenckel. Stewart has used two independent methods, a colorimetric and Hoppe-Seyler's chemical method. Fraenckel has used Bleibtreu's chemical method. The agreement between the results of Stewart and those of Fraenckel is very good. However, as has been stated also by Fraenckel, one would expect that Stewart's methods would give the most exact results. We shall, therefore, restrict ourselves to a comparison of the results of Stewart with those secured by the formula. In Table 1 is given a series of measurements made by Stewart[14] for the blood of a dog. The volume concentration of the normal blood was determined twice by the colorimetric method and twice by Hoppe-Seyler's method. The results were 41.16, 40.72, 41.52 and 40.99 per cent, the average ratio being 40.98 per cent. A series of red corpuscle suspensions of varying volume concentration was made up by concentration or dilution of the normal blood. The volume concentration for each of these suspensions was determined volumetrically using the value of the volume concentration of the original blood. These volume concentrations are given in Table I under ρ (obs.). The ratio of the conductivity of the serum to that of the blood is given under k_1/k.

TABLE 1

Conductivity of Blood of Dog

k_1/k	ρ observed *per cent*	ρ calculated *per cent*	Difference *per cent*
15.62	90.7	88.2	+ 2.7
9.08	82.1	80.5	+ 2.0
6.56	74.5	74.0	+ 0.7
5.06	67.8	67.5	+ 0.4
4.14	61.6	61.6	— 0.0
3.51	56.1	56.2	— 0.2
3.063	51.0	51.4	— 0.8
2.726	46.4	46.9	— 1.0
2.436	42.2	42.3	— 0.2
2.348	41.0	40.8	— 0.5
2.225	38.4	38.5	— 0.4
1.903	31.9	31.6	— 0.8
1.697	26.4	26.3	— 0.0
1.539	21.8	21.6	+ 1.0
1.428	18.1	18.0	+ 0.5
1.342	15.3	14.9	+ 2.4
1.232	11.4	10.7	+ 6.1

[14] G. N. Stewart, *J. Physiol.*, 24, 356 (1899).

In applying our formula, we take $k_2 = 0$, and assume $a/b = 1/4.25$; consequently $x = 1.05$ and $\beta = -1.95$, and either (15) or (17) may be used to calculate the values of the volume concentration ρ for the observed values of k_1/k. These are given under ρ (calc.). The deviations ρ (obs.) $- \rho$ (calc.) given in the fourth column are probably always within the experimental errors.*

It may be of interest to apply our formula also to some measurements of sand suspensions which have been made by Oker-Blom,[15] and are often cited in connection with work on the conductivity of blood. Two different kinds of sand were used. The suspensions were prepared by adding the sand to a hot salt solution containing 3 per cent gelatine and cooling this mixture to gelatination

TABLE 2

Conductivity of Suspensions of Sand

k_1/k observed	ρ observed *per cent*	β	x
2.488	40.	2.22	.820
2.220	36.4	2.14	.876
2.075	33.3	2.15	.870
1.952	30.8	2.14	.876
1.866	28.6	2.17	.854
1.790	26.7	2.17	.854
1.725	25.0	2.18	.848
1.6835	23.5	2.22	.820
	Average values:	2.17	.854

under continuous rotation. No information is given concerning the form of the sand particles except for the statement that the particles of the sand which were used in the second series of experiments (Table 3) were more nearly spherical than those which were used in the first series (Table 2). Our theory is therefore best applied by using Oker-Blom's observed values of k_1/k and ρ and calculating the value of x by means of Eq. (17) since

* The red corpuscles of mammalians according to the most generally accepted data are biconcave in shape but their dimensions especially in the dog have not been accurately measured. The value 1/4.25 for a/b which secures the best agreement in the present case is in good agreement with the observed values for the dimensions. Determinations of the conductivity of the blood of different animals with simultaneous measurements of the dimensions of the red corpuscles will be made in this laboratory; these investigations will include studies of the blood of different non-mammalian vertebrates in which the red corpuscles are approximately ellipsoids.

[15] M. Oker-Blom, *Arch. Ges. Physiol.*, **79**, 510 (1900).

$k_2 = 0$. Our calculated results are given in Tables 2 and 3, one for each of the two kinds of sand used by Oker-Blom. The calculated values for x in each case are constant within experimental errors. It hardly seems probable, however, that the sand

TABLE 3

Conductivity of Suspensions of Sand

k_1/k observed	ρ observed *per cent*	β	x
1.190	10	1.710	1.410
1.426	20	1.705	1.420
1.734	30	1.712	1.405
2.156	40	1.732	1.367
2.715	50	1.715	1.400
3.613	60	1.74	1.35
	Average values:	1.72	1.392

particles could have been as flat as these values for x would indicate; it is more probable that the large values for x are due to the fact that the sand particles became more or less completely orientated by the rotation. Eq. (14) with a different value for x holds also in this case.

A MATHEMATICAL TREATMENT OF THE ELECTRIC CONDUCTIVITY AND CAPACITY OF DISPERSE SYSTEMS

II. The Capacity of a Suspension of Conducting Spheroids Surrounded by a Non-Conducting Membrane for a Current of Low Frequency [1]

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INTRODUCTION

In the following discussion the specific electric capacity of a disperse system is defined as that capacity which when combined in parallel with a certain resistance electrically balances one centimeter cube of the system. The present discussion applies to the case in which the capacity is due to phenomena at the interphases of the system, especially as in biological tissues, the capacity of which, as is well known, is usually very high. The capacity may be due to either or in part to each of two different causes: (1) a polarization at the interphases, and (2) the presence in the interphases of thin poorly conducting membranes which act as static condensers. The calculation presented here applies to the first case only if the polarization resistance is small compared to the impedance of the polarization capacity. The general case, when they are of the same order of magnitude, will be considered in Part III of this series of papers.

In this presentation we shall derive a formula by which we can determine from the capacity and resistance of a suspension of spheroids and their geometrical form the capacity per unit of surface of the suspended particles. One interesting application of the formula is the calculation of the thickness of the membrane when the capacity is due entirely to the static capacity of membranes on the surface of the suspended particles. As will be shown in the following paper, this condition is probably realized for the case

[1] For Part I, see p. 341.

of blood, and, accordingly, we derive the value of about $3 \times (10)^{-7}$ cm. as the thickness of the membrane, which surrounds the red corpuscle, using a probable value for the dielectric constant of the membrane. This method will probably be useful also for the case of many non-biological suspensions, such as graphite suspensions, which contain well conducting particles surrounded by poorly conducting films, produced by chemical or adsorptive processes.

The fact that capacity of the type here considered is mainly dependent on the state of the interphases, makes it probable that this may be an important characteristic of the colloid properties of the system; especially may we expect this to be true for the case of biological systems. As a matter of fact, investigations which have been carried out in this laboratory have confirmed this belief. It may, for instance, be mentioned that it is found that the capacity of a tumor bears a rather constant relation to its malignancy, this relation appearing so constant that it seems probable that the measurement of the capacity may provide a very practical method for diagnosing the malignancy of a tumor.

MATHEMATICAL THEORY

We shall first consider the case of a suspension of particles of any form (volume concentration being ρ, and number of particles per cc being n), each particle in which is surrounded by a non-conducting membrane of uniform thickness t, and uniform dielectric constant K. The capacity of this membrane per square centimeter is $C_0 = K/4\pi t) \cdot (10^{-5}/9)\mu f$. The resistance of the interior of a particle for the frequencies to be considered is supposed to be small compared with the impedance represented by the static capacity of the surface membrane. We shall call the specific conductivity of the suspending medium k_1 and of the suspension k. If furthermore, $\overline{F^2}$ is the average value of the square of the electric force in the suspending medium, we have

$$(1 - \rho) k_1 \overline{F^2} = k \quad V^2. \tag{18}$$

This equation expresses the fact that the heat developed in the suspension by the electric current is equal to the heat developed in a homogeneous conductor with the conductivity k for the same driving potential V. We shall now assume, following thereby in principle the method employed in Part I, that the average value of

electrostatic energy which is present at the surface of each suspended particle is obtained by placing the particle in a homogeneous field of force equal to $\sqrt{\overline{F^2}}$. Evidently this electrostatic energy is proportional to C_0 and to $\overline{F^2}$, say equal to $NC_0\overline{F^2}$; consequently we have, if C is the capacity of the suspension in microfarads,

$$\tfrac{1}{2}CV^2 = n\ N\ C_0\overline{F^2}. \tag{19}$$

By Eqs. (18) and (19)

$$C = 2N\,C_0\left(\frac{k}{k_1}\right)\left(\frac{n}{1-\rho}\right) \tag{20}$$

Here N is dependent only on the constants which define the single suspended particle geometrically.

We shall now proceed to calculate N for the case of a suspension of spheroids. The electric forces in the suspending liquid are obtained by means of the equations given in Part I using $k_2 = 0$. Since the potential inside the corpuscle is constant, the resistance of the inside of the corpuscle having been assumed low as compared with the impedance of the membrane, V_{int} of Eq. (6) Part I, represents the potential difference between the two sides of the membrane. The average total static energy at the surface of a spheroid, arbitrarily placed in a homogeneous field of strength unity is consequently

$$N\,C_0 = \int \frac{^0\cos^2\varphi d(2\pi\cos\varphi)}{4\pi} \cdot \tfrac{1}{2}C_0 \sum(\alpha = a, b, b) \int \frac{4x^2 dS}{(2 - ab^2L_a)^2}$$

φ being the angle between the direction of the field and one of the axes of the spheroid. Hence

$$NC_0 = \frac{2}{3}C_0\left[\frac{C_a}{4M^2} + \frac{2C_b}{(2-M)^2}\right]\frac{4}{3}\,\pi ab^2 \cdot a \qquad (a < b)$$

$$C_a = \int (\text{over surface of spheroid } x \neq a)\left(\frac{x^2 dS}{\frac{4}{3}\pi a^2 b^2}\right)$$

$$= \frac{3}{4}\left[1 + \frac{1}{2}\left(\frac{a}{b}\right)^2\frac{1}{e^2} - \frac{1}{2}\left(\frac{a}{b}\right)^4\frac{1}{e^3}\log\frac{b}{a}(1+e)\right] \quad (\text{when } a < b)$$

$$= \frac{3}{4}\left[1 - \frac{1}{2e^2} + \frac{1}{2}\,\frac{a}{b}\,\frac{1}{e^3}\arcsin e\right] \qquad (\text{when } a > b)$$

$$C_b = \int (\text{over surface of spheroid } x \neq b)\left(\frac{x^2 dS}{\frac{4}{3}\pi a^2 b^2}\right)$$

$$= \frac{3}{4}\left(\frac{b}{a}\right)^2 \left[1 + \frac{a}{b}\ \frac{1}{e}\log\frac{b}{a}(1+e)\right] - \frac{3}{8}\left(\frac{b}{a}\right)^2 \times$$

$$\left[1 + \frac{1}{2}\left(\frac{a}{b}\right)^2 \frac{1}{e^2} - \frac{1}{2}\left(\frac{a}{b}\right)^4 \cdot \log\frac{b}{a}(1+e)\right] \quad \text{(when } a < b\text{)}$$

$$= \frac{3}{4}\left(\frac{b}{a}\right)^2 \left[1 + \frac{a}{b}\ \frac{1}{e}\arcsin e\right]$$

$$- \frac{3}{8}\left(\frac{b}{a}\right)^2 \left[1\,\frac{1}{2e^2} + \frac{1}{2}\ \frac{a}{b}\ \frac{1}{e^3}\arcsin e\right] \quad \text{(when } a > b\text{)}$$

In these equations

$$e = \sqrt{1 - a^2/b^2} \quad (a < b); \qquad e = \sqrt{1 - b^2/a^2} \quad (a > b).$$

Consequently ($\frac{4}{3}\pi ab^2 n$ being equal to ρ),

$$C = \frac{4}{3} C_0 \frac{k}{k_1} \cdot \frac{\rho}{1-\rho} a \left[\frac{C_a}{4M^2} + \frac{2C_b}{(2-M)^2}\right]$$

(For the value of M see Part I, p. 348.)

By Eq. (13) $(k_2 = 0)$: $(\rho)/(1-\rho) = (k - k_1)/\beta k$. Introducing furthermore

$$\alpha = -\tfrac{4}{3}\beta \left[\frac{C_a}{4M^2} + \frac{2C_b}{(2-M)^2}\right] \left(\frac{a}{b}\right) \text{ (when } a < b\text{).}$$

$$\text{and } \alpha = -\tfrac{4}{3}\beta \left[\frac{C_a}{4M^2} + \frac{2C_b}{(2-M)^2}\right] \qquad \text{(when } a > b\text{),}$$

and substituting resistances (r, r_1) for conductivities (k, k_1) we obtain

$$C = \alpha\ (1 - r_1/r)\ q\ C_0 = C_{100}\ (1 - r_1/r) \qquad (21)$$

C_{100} being the (imaginary) capacity of the 100 per cent concentrated suspension, or

$$C_0 = \frac{C}{aq(1 - r_1/r)} \qquad (22)$$

in which $2q$ represents the major axis of the spheroid. The values

TABLE I

Values of α as a function of b/a and of a/b.

b/a:	1	2	3	4	∞
α:	1.50	1.30	1.27	1.28	1.65
a/b:	1	2	3	4	∞
α:	1.50	1.03	0.94	0.94	$(.118 \times a/b)$

of α are given for different values of b/a in Table I. An experimental verification of the formula will be presented in the following paper (p. 357).

THE ELECTRIC CAPACITY OF SUSPENSIONS OF RED CORPUSCLES OF A DOG

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The following experiments illustrate the application of the theory which was presented in the preceding paper (p. 353) and confirm it.

The capacity, which for a one centimeter cube of normal blood is of the order of a few hundred micromicrofarads in parallel with a resistance of a few hundred ohms, was measured with a specially designed bridge over a range of frequencies from 800 to 4,500,000 cycles. The sensitivity of the bridge is such that such a capacity can be measured with an accuracy of a few $\mu\mu$f at the lowest frequency. Two arms of the bridge contain a Kohlrausch slidewire which is always used near its middle point; the third arm contains a decade resistance box R_1 (General Radio Company) with a decade condenser in parallel, and the fourth arm the electrolytic cell with a variable condenser C_r (General Radio standard condenser) in parallel. By means of a switch the electrolytic cell can be replaced by a decade resistance box R_r similar to R_1. The coils in the resistance boxes are wound by the Ayrton-Perry method and their effective inductances are rather low.

The current to the bridge is delivered by an audion oscillator and the heterodyne method of detection is employed, using three stage amplification. The bridge is connected to generating and heterodyne oscillation and to the detector tube by very loose inductive couplings. The electrolytic cell has the form of an hour-glass with large platinized platinum electrodes sealed into the glass at the ends; it is designed to have the lowest possible amount of polarization at the electrodes. The electrode area is between 10 and 20 cm^2; the distance between the electrodes between 5 and 10 cm. The cell constant is about 1. Effective stirring, which is essential, is accomplished by gently blowing through two glass tubes which are sealed to the top of the cell.

The abstract of the protocol, given in Table I, will explain the experimental procedure. The cell filled with the suspension is compared with the resistance box R_r; the difference between the settings

TABLE I

Partial abstract of protocol for blood (11.1%)

	Units	Exp. IV$_1$		Exp. IV$_2$		Diluted serum	
R_1' (cell in)	ohms	93.3		93.2		93.1	
C_r'	arb.	6.47		6.61		8.08	
Setting of slide wire		+1		+7		−1	
R_r'' (R_r instead of cell)	ohms	93.9	93.8	93.7	93.6	93.7	93.8
C_r''	arb.	10.05	10.43	10.26	10.68	10.72	10.40
Setting of slide wire		−14.5	+7	+2.5	+24.5	0	−17.5
Temperature		23.30°	.....	23.20°	.....	22.40°	.....
$C_r'' - C_r'$	μμf	217	240	222	247	160	141
Total inductance L	10^{-10}h	11790	11650	11480	11300	11480	11650
Equivalent capacity $(L/R_r''^2).10^3$	μμf	134	132	130	129	130	132
Capacity corrected for inductance	"	83	108	92	118	30	9
Corrected for difference in slide-wire setting	"	101		97		29	
Corrected for static capacity of electrolytic cell	"	95		91		21	
Capacity for cell filled with serum	"	21		21			
Capacity of blood	"	74		70			

of the condenser C_r, $(C_r'' - C_r')$, gives an uncorrected value for the capacity of the suspension. This value is first corrected for the inductance of the coils used in the resistance box R_r and for the difference between the inductances of the leads which connect the cell and R_r respectively to the bridge; this correction for our case is (L/R_r^2) farad, when this total inductance L is in henries. A small correction is thereafter introduced for the static capacity of the electrolytic cell, which, when filled with a homogeneous liquid of dielectric constant K, is $K/4\pi c'$ cm. in which c' is the cell constant equal to the ratio of resistance to specific resistance. For the case of a suspension with a non-conducting disperse phase, like blood, K is the dielectric constant of the suspending liquid (for blood therefore about 81) and c' is the constant of the electrolytic cell c times r/r_1, r and r_1 being the specific resistances of the suspension and the intracellular liquid. Consequently, the static capacity is $81/(4\pi c r/r_1) \times (10/9)$ μμf $= 7.2/(cr/r_1)$ μμf.

The value for the capacity thus obtained is still faulty, due to the difference in static coupling between the electrolytic cell and the other parts of the bridge on one side and on the other side between the resistance box R_r and the other parts of the bridge. The corresponding correction is obtained by making once for all a series of measurements with the cell filled with various dilutions of serum covering the total range of resistances used; the measured capacities are corrected as above and the values which vary very slowly with the resistance, are plotted against the resistance. From this curve a "zero value" for the capacity of the cell is found at the resistance observed in the case of blood which comprises the said difference in static coupling. This "zero value" is subtracted from the value for the capacity as obtained above.

The procedure described above would not have given a correct elimination of a polarization at the electrodes of the electrolytic cell if such an effect had been present to any appreciable amount within the experimental range of frequencies. The frequency at which the polarization becomes appreciable is easily determined by measuring the serum at decreasing frequencies; the setting of the standard condenser remains practically constant until the critical frequency is reached, when an abrupt change takes place.

A confirmation of the accuracy of this method was obtained by making measurements on cream, in which case the resulting capacity is zero. The fact that the value of the capacity of a corpuscle suspension is found to be independent of the form of the electrolytic cell and of the frequency serves as a further confirmation. (The capacity is found to be independent of the frequency between 3600 and 87,000 cycles per sec.; for higher frequencies the capacity decreases due to the fact that the impedance of the static capacity of the corpuscle membrane becomes comparable with the resistance of the corpuscle interior.)[1]

Tables II and III present the results of two series of measurements, typical of several, on the blood of a dog. They include corpuscle concentrations between 10 and 84 per cent. The stated volume concentrations were derived from the resistances by an earlier formula ($a/b = 1/4$). The capacity (C_{100}) for 100 per cent volume concentration is calculated by formula (21) of the

[1] H. Fricke and S. Morse, The electric resistance and capacity of blood for frequencies between 800 and 4,500,000 cycles. *Jour. Gen. Physiol.*, 1925, IX, 153-167.

TABLE II

Capacity of suspensions of red corpuscles of a dog in own serum

Defibrinated blood of dog No. 1 was concentrated by centrifugation, and the concentrated suspension was diluted with serum. Resistance r_1 of serum: 84.25 ohms; temperature: 18.95° C; constant of electrolytic cell: $\sigma = .98$.

Frequency: 87000 cycles per sec. Date: March 22, 1925.

Experiment	Volume concentration	Resistance r	Capacity C	C_{100} (calc.)	
	(per cent)	(ohms)	($\mu\mu$f)	($\mu\mu$f)	
I	83.9	931.0	374	411	Concentrated by centrifugation from original blood.
II	21.0	126.9	129	385	From 83.9 per cent suspension by dilution.
III	72.0	498.0	343	411	From 83.9 per cent and 21 per cent suspensions.
IV	47.5	230.2	237	374	From 72.0 per cent suspension by dilution.
V	60.2	329.0	286	385	From 83.9 per cent and 47.5 per cent suspensions.

TABLE III

Capacity of suspensions of red corpuscles of a dog in own serum

Defibrinated blood of dog No. 1 was diluted with own serum. Resistance r of serum: 75.8 ohms; temperature: 23.10° C; constant of electrolytic cell: .98.

Frequency: 87000 cycles per sec. Date: March 23, 1925.

Experiment	Volume concentration	Resistance r	Capacity C	C_{100} (calc.)	
	(per cent)	(ohms)	($\mu\mu$f)	($\mu\mu$f)	
I	43.9	188.7	232	388	Original blood.
II	30.8	140.1	172	374	From original blood by dilution.
III	20.6	113.7	126	378	From 30.8 per cent suspension by dilution.
IV	11.1	94.0	72	371	From 20.6 per cent suspension by dilution.
V	10.6	93.4	74	391	From original blood by dilution.
VI	42.8	185.3	221	374	Original blood.

Average: 380$\mu\mu$f $\pm$ 2 per cent.

preceding paper (p. 353). The values are constant for concentrations up to about 60 per cent; for still higher concentrations, which approach the stage of total packing for which the theoretical foundation for the formula may be doubtful, there may be a slight tendency to an increase. Using the lower concentrations alone, we obtain 380μμf as the average value of C_{100}. Since the constant of the electrolytic cell is .98 (= resistance/spec. resistance), the specific value of C_{100} (corresponding to a one centimeter cube) is $380 \times .98 = 372$ μμf.

Using $a/b = 1/4$ as in our earlier paper [2] and taking 7.2 $(10)^{-4}$ cm for the diameter $2q$ of the corpuscle, by formula (22) we obtain for the capacity per cm² of the membrane

$$C_0 = C_{100}/\alpha q = 372 \times 10^{-6}/(1.28 \times 3.6 \times 10^{-4}) = 0.81\mu f.$$

It has been shown elsewhere [1] that the capacity of blood is independent of the frequency between 3600 and 87,000 cycles per sec. For higher frequencies the capacity decreases; this decrease, however, for the experimental range of frequencies (up to 4,500,000 cycles), is satisfactorily explained as due to the impedance of the inter- and intra-cellular liquids, with which the capacity of the corpuscle membrane is in series, C_0 itself being independent of the frequency over the above range. We find also that the capacity is not changed when the corpuscles from defibrinated blood are suspended in Ringer's solution or in an isotonic solution of dextrose.

On the ground of our present, although rather incomplete, knowledge of polarization, such a constancy of the capacity would seem hardly possible if it were due to a polarization at the surface of the red corpuscle. Furthermore,[3] there is much evidence that the resistance of the membrane which surrounds the corpuscle is high as compared with the impedance of the capacity C_0 over our whole experimental range of frequencies; therefore, even with a constant polarization capacity at the surface of the corpuscle, the observed capacity should have decreased as the frequency increased. (The resistance of the membrane may, for instance, be estimated from known data for the diffusion of electrolytes from the serum into the corpuscle.) At present, therefore, it seems probable that the observed capacity is due to the static capacity of the corpuscle membrane. The order of magnitude of the thickness of this mem-

[2] H. Fricke, *Jour. Gen. Physiol.* 6, 741-746 (1924); *Phys. Rev.* 24, 575-587 (1924), Eq. (13).

[3] H. Fricke, The electric capacity of suspensions with special reference to blood, *Jour. Gen. Physiol.*, 1925, lx, 137-152.

brane, which may be derived on this assumption, is suggestive. By using a value of 3 as the dielectric constant of the membrane (a value which of course is rather uncertain, the more so, since the membrane appears to be monomolecular), we obtain a thickness of 3.3×10^{-7} cm. This value corresponds to a chain of from 20 to 30 carbon atoms. Thus, we evidently arrive at the conclusion that the membrane of the corpuscle is monomolecular.[3]

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